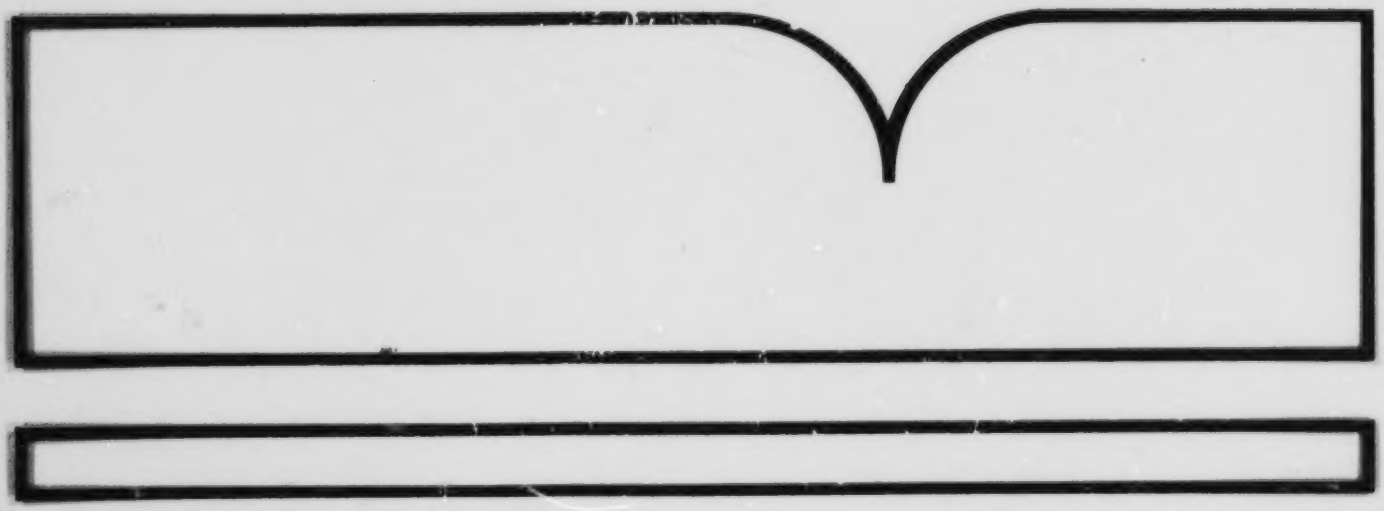
PB84-188887

Intrauterine Exposure of Humans to PCBs (Polychlorinated Biphenyls) Newborn Effects

Michigan Univ., Ann Arbor

May 84



U.S. Department of Commerce
National Technical Information Service
NTIS

BEGIN FIRST LINE OF TEXT HERE
. . TYPING GUIDE SHEET
CENTER OF PAGE
TOP OF IMAGE

PB84-188887

EPA-600/3-84-060
May 1984

DROPPED HEAD. BEGIN SECTIONS HERE

INTRAUTERINE EXPOSURE OF HUMANS TO PCBs:

Newborn Effects

Greta Fein[1], Joseph L. Jacobson[2], Sandra W. Jacobson[2] and Pamela Schwarz[1]

1. School of Public Health
University of Michigan
Ann Arbors, MI 48109

2. Department of Psychology
Wayne State University
Detroit, MI 48202

PS-CR-808520010

PROJECT OFFICER:

Nelson Thomas

ENVIRONMENTAL RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
DULUTH, MN 55804

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

BEGIN LAST LINE OF TEXT
3/8"
PAGE NUMBER
BOTTOM OF IMAGE AREA OUTSIDE DIMENSION FOR TABLES AND ILLUSTRATIONS
EPA-287 (Rev.3 (4-76))

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA-600/3-84-060		PB84 188887

4. TITLE AND SUBTITLE	5. REPORT DATE
Intrauterine Exposure of Humans to PCBs: Newborn Effects	May 1984
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
G. Fein, J. L. Jacobson, S. W. Jacobson, and P. Schwarz	
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
School of Public Health University of Michigan Ann Arbor, MI 48109	11. CONTRACT/GRANT NO.
	CR808520-01-0
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Environmental Research Laboratory Office of Research and Development U.S. Environmental Protection Agency Duluth, MN 55804	14. SPONSORING AGENCY CODE
	EPA/600/03

15. SUPPLEMENTARY NOTES

16. ABSTRACT

The effect of low-level chronic exposure to polychlorinated biphenyls (PCBs) from consumption of Lake Michigan fish was assessed in pregnant women and their newborn offspring. Low levels of PCBs remain in the human body for some time, and caused, in this sample, decreases in birth weight, head circumference, and gestational age of the newborn. PCBs appeared to be transmitted to the infants prior to birth through the maternal serum, and after birth through breast milk. Behavioral deficiencies were observed in the infants exposed to PCBs both in autonomic immaturity and depressed responsiveness.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
RELEASE TO PUBLIC	UNCLASSIFIED	88
	20. SECURITY CLASS (This page)	22. PRICE
	UNCLASSIFIED	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Intrauterine Exposure of Humans to PCBs: Newborn Effects

Greta G. Fein[1], Joseph L. Jacobson[2],
Sandra W. Jacobson[2], and Pamela W. Schwartz[1]

Final report Submitted to the U.S. Environmental Protection Agency
February, 1983

This research was funded under grant #CR808520010 from the United States Environmental Protection Agency. We wish to thank Wayland R. Swain and Nelson A. Thomas of the EPA Large Lakes Research Station and Harold E. B. Humphrey of the Michigan Department of Public Health for their generous assistance in the development of this project. We also wish to thank Harold A. Price, Michael D. Mullin, and Janet Eyster for their many helpful suggestions regarding the analysis of biological data and Joel Ager for his suggestions regarding the statistical analysis of the data. We greatly appreciate the assistance of Carol Alexander, Gail A. Brumitt, Gwen Hendrickse, and Patricia Yaros in the collection of the data; Jeffrey K. Dowler and Gregory A. Proulx in data analysis; and Carol Stanik and Maria Petkoff in preparation of this manuscript. Finally, without the cooperation of physicians, hospital personnel, and parents in Grand Rapids and Muskegon, this study would not have been possible.

Polychlorinated biphenyls (PCBs) are organochlorine compounds. Their chemical properties, including a high dielectric constant and the ability to withstand high temperatures for long periods, have resulted in their utilization in a wide variety of manufacturing processes. A world wide pollutant, PCBs have been found in air, water and soil samples of industrialized countries (Carey & Gowen, 1976; Jelinek & Corneliussen, 1976; Veith & Lee, 1971; Young, McDermott & Heesen, 1976). Detectible levels of PCBs have also been found in tissue and blood samples of the general human population (Biros, Walker & Medbery, 1970; Yobs, 1972), and relatively high levels have been reported in human breast milk samples collected in Canada and the United States (Grant, Mes, & Frank, 1976; Musial, Hutzinger, Zitko & Crocker, 1974; Savage, Tessari, Malberg, Wheeler & Bagley, 1973).

Evidence from several sources indicates that PCBs cross the placenta and are teratogenic in human infants exposed at high levels. PCBs are found in umbilical cord serum at birth when exposure results from ordinary dietary sources, and maternal serum levels are moderately related to fetal serum levels (Kodama & Ota, 1980; Masuda, Kagawa, Kuroki, et al., 1978; Polishuk, Wasserman, Cucos & Ron, 1977). In separate incidents in Japan and Taiwan, infants of pregnant women who consumed rice oil accidentally contaminated with sizable amounts of PCBs showed elevated PCB serum levels and a set of physical characteristics (e.g., brown pigmentation of the skin, swollen eyelids) known in the literature as Yusho (rice oil) disease (Harada, 1976; Higuchi, 1976; Wong & Hwang, 1981). Infants exposed in utero were small-for-

gestational age and tended to be born prematurely (Funatsu, Yamashita, Ito, et al., 1972). Follow-up studies of exposed infants reported an average IQ of 70; sluggish, clumsy and jerky movement; apathy and hypotonia; autonomic disturbances; and growth impairment (Harada, 1976). These disturbances in responsiveness and neuromusclar organization are consistent with reports of slowed sensory and motor nerve conductance in exposed adults (Chia, Su, Chen, Wu & Chu, 1981; Harada, 1976). Although PCB blood levels diminish once exposure ceases, infants born several years after the exposure of their mothers showed elevated PCB blood levels, reduced birth weight, and brown pigmentation of the skin (Abe, Inoue & Takamatsu, 1975; Harada, 1976).

Placental passage and fetopathy have also been demonstrated in experimental studies with mammals such as rabbits, mice, rats, and rhesus monkeys (Allen, Barsotti & Carstens, 1980; Bowman, Heironimus & Allen, 1978; Chou, Miike, Payne & Davis, 1979; Masuda, Kagawa, Kuroki, et al., 1979; Grant, Villeneuve, McCully & Phillips, 1971; Tilson, Davis, McLachlan & Lucier, 1979). PCBs may cross the placenta more freely as gestation progresses. In mice, higher concentrations are found in the fetus, placenta, and amniotic fluid as parturition approaches (Torok & Weber, 1981).

In rhesus monkeys, prenatally exposed infants weighed less at birth than controls and by two months of age developed Yusho-like symptomatology. Behavioral tests given between 6 and 24 months of age revealed hyperlocomotor activity and learning retardation (Bowman, Heironimus & Allen, 1978), but when tested at 44 months of age, these animals were hypoactive relative to controls (Bowman & Heironimus, 1981). In a follow-up study, adult female monkeys were removed from their PCB diet for a one-year period

prior to conception (Allen et al., 1980). Although the physical condition of these animals improved and PCB levels in maternal adipose tissue declined markedly, four of the 15 offspring were stillborn. The birth weight of the liveborn infants was reduced relative to nonexposed infants, and four infants died after weaning at four months of age. In these studies, animals were fed diets containing only 2.5 or 5.0 mg/kg of PCBs, levels thought at the time to be low. In rhesus monkeys, as in humans (Harada, 1976), teratogenic effects appear in infants whose mothers had consumd PCB prior to, but not during, pregnancy.

When mice were fed relatively low levels of PCBs during pregnancy (32 mg/kg on days 10-16 post-conception), some pups subsequently developed the "spinning syndrome" (Chou et al., 1979; Tilson et al., 1979). More subtle signs of neurobehavioral dysfunctioning appeared in prenatally PCB-exposed mice which did not develop obvious clinical signs of neurotoxicity. Assessments of subtle behavioral functions indicate that exposed but apparently asymptomtic mice have learning deficits and depressed neuromuscular reflexes even though PCBs are no longer detectable in their body tissues (Tilson et al., 1979). A sluggish response to a novel situation and less pronounced habituation have been observed in asymptomatic mice exposed perinatally to PCB doses below those associated with obvious neuromotor disorders (Storm, Hart & Smith, 1981).

Table 1 summarizes the major assessment categories used in teratogenic assessment (Spyker, 1975) and the results of the studies reviewed above. While to date no morphological anomalies

have been found to result from fetal exposure to PCBs, such exposure has been associated with clinical symptoms, maturational and growth retardation, and a variety of subtle behavioral deficits.

Consumption of PCB-contaminated fish constitutes a major source of human exposure to PCBs, with PCB body burden directly related to amount of fish consumed (Humphrey, 1976; Kreiss, Zack, Kimbrough, Needham, Smrek & Jones, 1981). Although epidemiological studies of acutely exposed humans indicate that PCBs are injurious, there are problems in extrapolating from studies of humans acutely exposed at high levels to those exposed chronically at low to moderate levels. Even at relatively high levels of consumption of PCB-contaminated fish, short-term exposure is considerably less than that experienced in the rice oil incidents. In contaminated fisheaters, obvious and distinctive Yusho symptoms have not been noted, and infants born to mothers who consume contaminated fish are likely to be clinically asymptomatic. Analyses of the consequences are complicated because the effects of low level chronic exposure are likely to be subtle and may occur in the absence of symptoms typically associated with acute exposure.

Although subtle behavioral effects appear in animals exposed to low doses of PCBs, extrapolation from animals to humans is also risky. For example, species differ in their ability to eliminate PCBs, and as a result, the dose required to produce an effect will vary among species. Animal models are an essential aspect of teratogenic testing; however, the findings of this type of research must be corroborated in studies of humans.

Table 1

Assessment Categories in the Evaluation of Teratogenic Effects

Assessment category	Illustration
1. Morphological characteristics	Anomalies not found in PCB studies
2. Physical characteristics	Chloracne; brown pigmentation of skin, lips, gums; parchment-like skin; swollen eyelids, face; premature eruption of teeth
3. Maturational landmarks	Preterm birth (neuromuscular and physical immaturity)
4. Growth	Small birth size; depressed postnatal growth
5. Reflexes	"Spinning syndrome" in mice
6. Activity levels	Hypo- and hyper-activity in an open-field; clinical assessment of apathy
7. Neuromuscular and sensory motor capacities	Tests of coordination (swimming in mice)
8. Sensory and attentional functions	Deficits in visual, auditory or olfactory attentional functions not found; numbness reported in humans exposed in adulthood
9. Learning ability	Alteration and reversal learning deficits in monkeys
10. Autonomic regulation	Inappropriate response to stress; deficits in temperature control; tremulousness
11. Sexual development	Reproductive failure; menstrual irregularities

The present study involves two groups of humans who are particularly at risk: the pregnant woman and her newborn offspring. The study, which utilizes a prospective longitudinal design, investigates the model shown in Figure 1. In this model, consumption of contaminated lake fish, assumed to be a major source of PCB exposure, results in elevated maternal PCB levels. Elevated maternal body burden has both direct and indirect implications for the developing fetus. Since PCBs cross the placenta, the developing fetus is exposed directly to some part of the mother's body burden. Maternal body burden may also affect maternal health and reproductive capacity, which in turn may influence fetal development. PCBs are also transferred from maternal tissue to breast milk, which provides an additional source of direct exposure for breast-fed infants.

In this report, relations among various measures of exposure and newborn outcomes are of special interest. First, measures of exposure are examined to validate linkages between contaminated fish consumption and elevated maternal PCB body burden, and between PCBs in maternal serum and PCBs in cord serum. Then, three measures of exposure (fish consumption and PCBs in maternal and cord sera) are analyzed in relation to measures of newborn status.

Method

Subjects

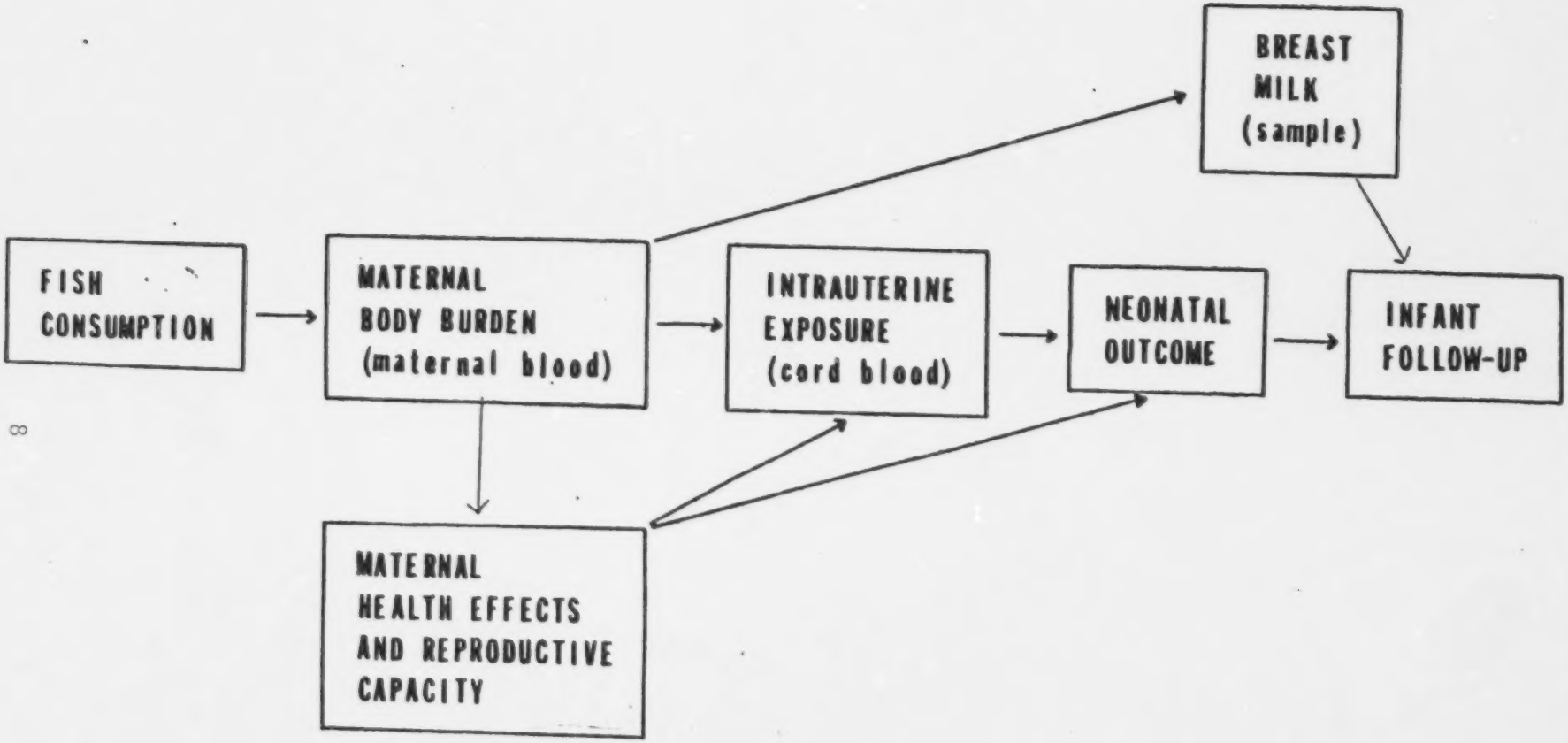


Figure 1. Model of pre- and postnatal exposure to polychlorinated biphenyls via ingestion of contaminated fish.

The sample, comprised of 313 newborn infants and their mothers, was drawn from three hospitals in Grand Rapids and one in Muskegon.[4] All mothers delivering at these hospitals were considered eligible to participate with the following exceptions: mothers had to be at least 18 years of age and have completed 10th grade in high school.

The infant sample consisted of 164 males and 149 females. The proportion of males (52%) did not differ significantly from expected (51%). All infants were white, with the exception of two black infants. Forty-three percent were first-borns. Six were the larger members of twin pairs, none of whom died during infancy. Anthropometric measures and demographic characteristics are presented in Table 2. Only one infant was below the tenth percentile on weight-for-gestational age (Lubchenco, Hansman, Dressler & Boyd, 1963). One severely premature newborn (GA = 26.9 weeks, birth weight = 909 gm) died. When the health status of the sample was evaluated on the Postnatal Complications Scale (Littman & Parmelee, 1974b),[5] the mean score was 94.1 percent optimal. Only five infants (2.1%) had a 5-minute Apgar score below 7.

Socioeconomic status (SES) of the study sample, based on a weighted sum of father's education and occupational status (Hollingshead, n.d.),[6] was predominantly middle-middle class. Most of the fathers' occupations ranged from semi-skilled

Table 2

Characteristics of the Sample at Birth (N=313)

	Mean	(SD)	Range
Infant characteristics			
Birth weight (gm)	3502.7	(560.3)	909.1 - 5028.9
Crown-heel length (cm)	51.1	(2.5)	28.5 - 56.0
Head circumference (cm)	35.1	(1.4)	30.5 - 41.3
Ponderal index[a]	2.7	(0.3)	1.9 - 5.6
Gestational age (weeks)[b]	40.4	(3.0)	24.3 - 45.9
Apgar scores			
1-minute	7.9	(1.3)	1.0 - 9.0
5-minute	8.9	(0.8)	2.0 - 10.0
Postnatal Complications score[c]	0.9	(0.1)	0.2 - 1.0
Family characteristics			
Socioeconomic status (SES)[d]	39.3	(13.5)	14.0 - 66.0
Maternal age	26.1	(4.6)	18.0 - 42.0
Maternal education (years)	13.3	(1.9)	10.0 - 19.0
Marital status (married)[e]	283.0	(90.4)	--
Obstetrical Complications score[f]	84.0	(0.1)	0.6 - 1.0

[a]Based on equation (Miller & Hassanein, 1971): $\frac{\text{birth weight (gm)} \times 100}{\text{crown-heel length (cm)}^3}$.

[b]Based on reported last menstrual period.

[c]Based on Postnatal Complications Scale (Littman & Parmelee, 1974b).

[d]Based on Hollingshead index (n.d.).

[e]N is presented rather than mean; percent of women married is in parentheses.

[f]Based on Obstetrical Complications Scale (Littman & Parmelee, 1974a).

laborers to middle-level management, with only 4.5 percent classified as menial or unskilled. Almost all of the women were married and living with the father of their newborn infant.

The sample was also homogeneous in terms of maternal education and age. Only 7.7 percent of the mothers failed to complete high school, while 18.2 percent completed college. Eighty-one percent were between 18 and 30 years of age and only 3.2 percent over 35. Fifty-seven percent attended prenatal birth classes; 95.8 percent began prenatal medical care by the fourth month of pregnancy, and the remaining 13 women by the sixth month. Their scores on the Obstetrical Complications Scale (Littman & Parmelee, 1974a)[7] ranged from a minimum of 63 percent to a maximum of 98 percent optimal, with a median of 85 percent optimal, suggesting little variability in obstetrical history.

The sample was selected to overrepresent women who had consumed Lake Michigan fish during some time in their lives. The majority (77%) reported consuming moderate to large quantities of Lake Michigan fish, while the rest (23%) reported consuming none of these fish. This design permits two types of analyses. First, adverse effects can be identified by comparing women who consume Lake Michigan fish with those who do not. Additional analyses can be performed to determine the statistical magnitude of the toxic effects and the particular dose-response relationships.

Procedure

Preliminary Screening

To ensure participation of infants likely to have been exposed *in utero* to a broad range of PCB levels, women were screened for past and present consumption of Lake Michigan fish on the morning following delivery. A questionnaire was used to ascertain the source,[8] amount, and kind of fish consumed in the year prior to the infant's birth, and the number of years of fish consumption at that rate. Women were also asked if there was a time in the past (dating back to 1966) when they ate greater amounts of Lake Michigan fish (e.g., the woman grew up in a family in which the father was a sports fisherman). If so, the amount and kind of fish consumed in the past, as well as the number of years of consumption at that rate, were recorded.

Sampling for contaminants in Lake Michigan fish has shown that most species tested contain detectable levels of PCBs, with especially high levels in fatty species, such as salmon and lake trout (International Joint Commission, 1978; Swain, 1981; Willford, Hesseburg & Nicholson, 1976). These fish, although high in contamination, may be eaten in small quantities, while other less contaminated fish, such as perch or smelt, may be eaten in large quantities. To obtain a more accurate measure of contaminated fish consumption, a weighted value was assigned to each fish species based on average contaminant levels for that species (Table 3). The range of values was normalized to lake trout, salmon, carp, and catfish, species containing the highest concentrations of PCBs, e.g., a fish having half the average PCB level of salmon or lake trout would be weighted 0.5.

Table 3

Relative PCB Values of Lake Michigan Fish

Type of fish	PCB weights
Chinook salmon	1.0
Coho salmon	1.0
Lake trout	1.0
Carp	1.0
Catfish	1.0
Bullhead	0.6
Pike or pickerel	0.6
German brown trout	0.4
Perch	0.4
Walleye	0.4
White sucker	0.4
Alewife	0.3
Burbot (lawyer)	0.2
Steelhead or rainbow trout	0.2
Brook trout	0.2
Menominee (round whitefish)	0.1
Smelts	0.1
Whitefish and chubbs (herring)	0.1

Note. Derived from data supplied by the Large Lakes Research Station, U.S. Environmental Protection Agency, Grosse Ile, Michigan.

The following equation was used to estimate the mother's annual rate of consumption for each type of fish:

RELATIVE PCB FISH WEIGHT	X	NUMBER OF FISH MEALS/YEAR	X	0.23 KG (1 FISH MEAL)	=	PCB-KG PER YEAR

This measure is summed across species for each individual to determine a woman's annual fish consumption rate. To estimate cumulative exposure, annual PCB-fish consumption rate was multiplied by the number of years the mother reported eating contaminated fish at that rate. If she reported eating contaminated fish at a higher rate in the past, the number of years at the current and past rates were determined separately and then multiplied by their respective consumption rates to yield a measure of cumulative exposure as follows:

	PCB KG/ YEAR	X	NUMBER OF YEARS AT PRESENT RATE	+	PCB KG/ YEAR	X	NUMBER OF YEARS AT PAST RATE	=	CUMULATIVE CONSUMPTION PCB-KG
PRESENT				PAST					

Sampling Criteria: Exposed and Unexposed

Two criteria were used to determine inclusion of women in the study: (1) If cumulative exposure within a 6-year period reported by the mother was equal to 11.8 kg (26 pounds) or more of contaminated fish, the mother qualified for inclusion in the study. This criterion was based on evidence that PCBs are retained in body tissues over relatively long periods of time

(Humphrey, 1976). (2) In addition, a control group was selected comprised of newly-delivered mothers who reported consuming no Lake Michigan fish in the past or during pregnancy.

Of the 8482 women screened (i.e., 96 percent of all maternity patients in the four participating hospitals), about 4 percent or 343 ate PCB-fish in sufficient quantities to qualify for inclusion in the exposed group.[9] About 29.3 percent of the women screened reported eating no Lake Michigan fish; 4.6 percent or 114 of these women were invited to serve as controls. As a check on whether women invited to participate in the study, either as fish-eaters or as controls, were similar demographically to women who were not asked to participate, a demographic comparison group was selected by matching each potential participant with the next woman whose screening interview followed her own. This procedure assured a comparison group matched for hospital and approximate date of delivery with the potential sample of exposed and nonexposed mothers. Women invited to participate did not differ significantly from others in their community in socioeconomic status, maternal age, education, marital status, or sex of infant (Table 4). Among those women invited to participate, fish-eaters did not differ from control women on these variables (Table 5).

Table 4

Comparison of Qualifiers and Demographic Comparison Groups (N=914)

	Qualifiers: Exposed and control groups (N=457)		Demographic comparison group (N=457)		
	Mean	(SD)	Mean	(SD)	t
Socioeconomic status (SES)[a]	38.5	(13.1)	37.6	(12.9)	1.10
Maternal age	25.9	(4.5)	25.9	(4.8)	0.05
Maternal education (years)	13.2	(1.9)	12.9	(2.0)	1.88
	N	(%)	N	(%)	χ^2
Marital status (married)	419	(91.7)	413	(90.4)	0.18
Sex of infant (male)	224	(49.6)	241	(53.9)	1.71

Note. Data on SES, maternal age, and sex of infant were unavailable as follows: SES was unavailable for eight qualifiers and ten comparison women; sex of infant for five qualifiers and ten comparison women; maternal age for one comparison woman.

[a]Based on Hollingshead index (n.d.).

Table 5

Comparisons of Qualifying Exposed and Control Groups (N=457)

	Qualifying Exposed Group (N=345)		Qualifying Control Group (N=112)		
	Mean	(SD)	Mean	(SD)	t
Socioeconomic status (SES)[a]	38.3	(13.1)	39.4	(13.2)	-0.76
Maternal age	26.0	(4.6)	25.4	(4.3)	1.33
Maternal education (years)	13.1	(1.9)	13.2	(1.9)	-0.44
	N	(%)	N	(%)	χ^2
Marital status (married)	319	(92.5)	100	(89.3)	1.12
Sex of infant (male)	167	(49.4)	54	(49.5)	0.00

Note. Data were unavailable on SES for six exposed and two control women; sex for seven exposed and three control infants.

[a]Based on Hollingshead index (n.d.).

Of the 457 women invited to participate, 144 (32%) refused. Mothers who consented to participate were more educated than refusers, suggesting that greater education may be associated with greater interest in research. Among women who agreed to participate, exposed and non-exposed control groups did not differ in socioeconomic status, maternal age or education, number of offspring (parity), or sex of infant (Table 6). While slightly more of the exposed women were married, this difference was not statistically significant ($p > .05$).

Measures of Exposure

PCB-fish consumption. The principal measures of contaminated fish consumption were: (1) highest annual rate of PCB-fish consumption; (2) cumulative PCB-fish consumption; and (3) rate of PCB-fish consumption during pregnancy. These measures were weighted for the contaminant levels of the species reported by the mothers. The first measure (highest annual rate) reflects findings from previous studies that the highest level of contaminated fish consumption predicts subsequent PCB serum levels (Humphrey, 1976), findings consistent with the tendency of PCBs to be poorly metabolized. But PCBs tend to accumulate in body tissues over time, and prediction might be improved when

Table 6

Study Sample: Exposure and Control Groups (N=313)

	Exposure group (N=242)		Control group (N=71)		
	Mean	(SD)	Mean	(SD)	t
Socioeconomic status (SES)[a]	39.3	(13.6)	39.5	(13.4)	-0.14
Maternal age	26.2	(4.7)	25.7	(4.5)	0.81
Maternal education (years)	13.3	(1.9)	13.3	(2.0)	0.15
	N	(%)	N	(%)	χ^2
Marital status (married)	223	(92.1)	60	(84.5)	3.70
Sex of infant (male)	124	(51.2)	40	(56.3)	0.39
Parity (first-borns)	100	(42.2)	32	(45.1)	0.18

[a]SES, based on Hollingshead index (n.d.), was unavailable for three exposed women.

reported values and years at these levels are taken into account. The measure of cumulative PCB-fish consumption, which sums rates over years after normalizing each component of the measure to z scores, was constructed to assess this possibility. The third measure, rate of PCB-fish consumption during pregnancy, was used to assess a somewhat different possibility, i.e., that the impact on the infant is especially pronounced when the mother consumes contaminated fish during pregnancy. PCB-kg refers to a fish consumption score weighted by the contaminant levels of the species reported by the mother. Mean annual rate of PCB-fish consumption at the highest levels reported by the exposed mothers was 6.7 PCB-kg (14.7 PCB-pounds) per year (SD = 5.8 PCB-kg, range = 1.2-41.7). This rate is equivalent to about 0.6 PCB-kg per month or 2-3 salmon or lake trout meals (at 0.2 kg per meal). The women reported eating Lake Michigan fish for an average of 16.1 years (SD = 9.0, range = 1.0-40.0). In the year preceding the infant's birth, mean level of fish consumption was 4.4 PCB-kg (9.7 PCB-pounds; SD = 4.4 PCB-kg, range = 0.0-26.5). Therefore, the selection procedure described earlier yielded a range of exposure levels with specific values depending on the particular measure of maternal fish consumption used. The fish consumption variables were positively skewed and were normalized by means of log transformations. One outlier, a woman who reported ingesting 54.5 kg of contaminated fish in one year, was eliminated from the analyses.

Laboratory Analyses

Hospital personnel collected samples of umbilical cord blood for every infant born in the participating hospitals at the time of delivery. Cord blood specimens for newborns in the sample were available, therefore, for laboratory analysis, while those of non-participants were discarded shortly thereafter. Samples of maternal blood were collected on the second day following delivery, as part of routine blood tests. Sixty-one percent of the infants in the sample were breast-fed, and of those, 70.3 percent of the mothers provided breast milk samples between 1-16 weeks after delivery. A second sample of breast milk was collected from 45 women who continued breast-feeding at 5 months.

Analyses of cord serum, maternal serum, and breast milk samples for PCBs were performed at the Michigan Department of Public Health by means of packed column gas chromatography (Burse, Needham, Liddle, Bayse & Price, 1980). A 4-mL sample of serum was mixed with 2 mL methanol. This mixture was extracted with 5 mL hexane/diethyl ether (1:1, v/v) three times by agitating on a rotary mixer 15-20 minutes at 50-55 rpm. The extracts were combined in a Kontes concentrator tube, reduced to a small volume (about 0.5 mL), and transferred quantitatively to a miniature Florisil cleanup column from which PBBs, PCBs, and chlorinated hydrocarbon pesticides were eluted with 6 percent diethyl ether/ petroleum ether mixture (v/v). The eluate was concentrated to a small volume (1.0 mL), transferred with three x 1.0 mL rinsings of hexane to a column of Silica Gel 60, and eluted with hexane to separate PCBs from the chlorinated hydrocarbon pesticide group (Picer & Ahel, 1978). The fraction containing PCBs, PBBs, and DDE

was concentrated to 2 mL and analyzed by electron-capture gas chromatography with a 3 percent SE-30 column. Injector, initial column, final column, and detector temperatures were 240°C, 160°C, 210°C, and 320°C, respectively. Quantification was provided by adapting the Webb-McCall method (Sawyer, 1978; Webb & McCall, 1973) to a computer data system with Aroclors 1016 and 1260 used as calibration standards. Estimation of PCB levels in sample extracts was based on comparison of peaks on the chromatogram with respective peaks of known concentrations in the reference standards. The Aroclor 1016 portion of the chromatogram was used to estimate the quantity of lower chlorinated congeners, while the 1260 portion was applied to measure levels of more highly chlorinated congeners and isomers. Limits of detection were 5 ng/mL for Aroclor 1016 and 3 ng/mL for Aroclor 1260 in the sample extracts. Quality control over time was ensured by addition of a spiked sample of bovine serum with every batch of ten samples, as well as the use of a glassware blank and a reagent blank. Serum lipids were determined colorimetrically using the Dade Total Standard for plotting the calibration curve of concentration vs. absorbence (Fringe, Ferdley, Dunn & Queen, 1972).

A similar procedure was used in analyzing breast milk samples. A 5 g sample of breast milk in a screw-capped (teflon-lined) culture tube was mixed with 0.1 of potassium oxalate and 5 mL methanol. This mixture was extracted in the same manner as serum samples. Extracts were combined in a micro distilling assembly and concentrated to a small volume. Evaporation of

solvent from the concentrated extract was conducted in a small preweighed aluminum dish and the residue dried under vacuum in a desiccator. In contrast to serum analysis, wherein lipid levels were estimated, lipid content of the breast milk sample was determined gravimetrically. The lipid residue was then redissolved in a small amount of petroleum ether and transferred quantitatively to a miniature Florisil cleanup column. Subsequent procedures for serum were then applied to the breast milk analyses.[10] (For a review of technical problems associated with these analytical procedures, see IARC Monograph, 1978; Safe, Pochini, McCrindle & Romkes, Liddle, in press; Mullin, Safe, in press; Humphrey, 1976).

All serum samples containing lipid levels below 200 mg/dL were omitted from the data analyses, since measurement techniques were judged to be insufficiently sensitive to detect PCB levels at lipid values of this magnitude. The removal of three maternal serum and 43 cord serum samples for this reason did not alter the fundamental nature of the PCB distribution. Twenty-seven additional cord blood samples could not be analyzed because insufficient quantities had been collected, the hospital had mistakenly discarded them, or because of equipment failures in the laboratory. Included in the following analyses were 198 cord

Infant Measures

There were four primary considerations in selecting infant outcome measures. First, there had to be evidence from studies of humans and animals that particular clinical symptoms, and maturational and other subtle functional disorders were associated with pre- or postnatal exposure to PCBs.

Second, measures selected had to have proven sensitive in discriminating various at-risk conditions and in detecting subtle behavioral effects.

Third, measures had to be comprehensive. Spyker's model of teratogenic effects suggests that in contrast to acute massive exposure which is associated with dramatic clinical disorders, longterm low-level exposure to a toxin produces subtle functional disturbances. Depending on genetic predisposition, the chemical involved, the dose and time of exposure, a variety of disturbances may occur. Assessments need to be comprehensive and include the various domains in which teratogenic deficits appear in different species.

Fourth, measures of infant and maternal health and background have to be complete enough to permit identifying correlates of PCB exposure so that potential confounding variables, such as maternal health, social class, parity, exposure to other drugs and anesthesia, can be statistically controlled.

The principle dependent measures include: (a) three anthropometric measures--birth weight, crown-heel length, and head circumference; (b) two estimates of gestational age, one using an observational technique developed by Ballard, Novak, and Driver (1979) and the other based on the mother's report of her last menstrual period prior to pregnancy; and (c) a behavioral assessment of the newborn based on the Neonatal Behavioral Assessment Scale (NBAS) (Brazelton, 1973).

Birth weight was obtained from the infant medical record. Because hospital measures of crown-heel length and head circumference were less strongly correlated with birth weight than our own assessments (r = .66 vs. .75 and .29 vs. .68, respectively), these measures were obtained from our examination performed during the second day following delivery.

The Ballard Examination for Fetal Maturity was administered to 220 infants at 20-53 hours of age. The remaining 93 infants were not tested because maternal consent could not be obtained within the limited time period during which the Ballard is considered reliable. The Ballard Scale correlates highly (r = .97) with the longer Dubowitz examination (Dubowitz, Dubowitz & Goldberg, 1970), on which it was based (Ballard, Novak & Driver, 1979). The Ballard, which takes an average of three as compared to the Dubowitz' nearly seven minutes to administer, omits items found to be unreliable, especially for sick newborns.

The Brazelton Neonatal Behavioral Assessment Scale (NBAS) evaluates the infant's response to increasing levels of external stimulation. Although new, the NBAS has emerged as a useful technique for assessing neonatal functioning and detecting a variety of at-risk conditions, such as pre- and post-maturity (Field, Hallock, Ting, Dempsey, Dabiri & Shuman, 1978), low birth weight (Als, Tronick, Lester & Brazelton, 1979), exposure to obstetrical medications (Aleksandrowicz & Aleksandrowicz, 1974), and methadone treatment (Strauss, Lessen-Firestone, Starr & Ostrea, 1975). It has also proven effective in predicting

interactive and attachment behavior during the first year (Field, Dabiri, Hallock & Shuman, 1977; DiVitto & Goldberg, 1979; Vaughn, Taraldson, Crichton & Egeland, 1980) and performance on measures of subsequent intellectual functioning (Powell, 1974; Sameroff, Krafchuk & Bakow, 1978), especially when used in connection with other risk factors (Field, Hallock, Ting, Dempsey, Dabiri & Shuman, 1978; Field, Demsey & Shuman, 1981).

The NBAS was administered to 287 newborns. In all but three instances (98% of the cases), testing was performed on the third day after birth (i.e., at 48-72 hours). In addition, the testing of one premature was delayed until the infant reached the conceptual age of 37 weeks, the earliest age at which the NBAS is considered valid.

The NBAS consists of 27 nine-point scales and 17 reflexes (Brazelton, 1973; Als, Tronick, Lester & Brazelton, 1979). In order to enhance reliability of measurement and to decrease the likelihood of chance findings resulting from an excessive number of comparisons, the 44 NBAS items were reduced to seven summary clusters. These clusters were derived by synthesizing the results of factor analyses from studies of six independent samples, including our own (Aleksandrowicz & Akelsandrowicz, 1976; Kaye, 1978; Osofsky & O'Connell, 1977; Sameroff, Krafchuk, & Bakow, 1978; Streissguth, Martin & Barr, 1977; see Jacobson, Fein, Jacobson & Schwartz, in press, for a more detailed review of procedures used in deriving these clusters). The clusters described in Table 7, which generally resemble the seven clusters suggested by Lester, Als, and Brazelton (1982), regroup those

Table 7

NBAS Items Included in the Seven Clusters

Clusters	
Response decrement	Light Rattle Bell Pin prick
Orientation	Inanimate visual Inanimate auditory Inanimate visual and auditory[a] Animate visual Animate auditory Animate visual and auditory
Tonicity	General tonus Pull-to-sit Defensive movements Activity
Range of state	Peak of excitement Rapidity of build-up Irritability Lability of states
Regulation of state	Self-quieting activity Hand-to-mouth facility
Autonomic maturity	Tremulousness[b] Amount of startle[b] Motor maturity
Reflexes	Total number of abnormal reflex scores

[a]Added in the present study from the NBAS-K (Horowitz, Sullivan, and Linn, 1978).

[b]Recoded to reverse the scale's direction, so that a high degree of tremulousness or startle receives a low score.

items which did not co-occur in these samples as initially predicted. High scores on the response decrement, orientation, tonicity, regulation of state, and autonomic maturity clusters represent more optimal behavior. A high score on the range of state cluster indicates a combination of greater lability and more intense arousal. A high score on the reflex cluster indicates a greater number of abnormal reflexes.

Control Variables

A comprehensive list of 68 potential confounding variables was assembled to test whether the observed relationships are spurious and attributable to factors other than PCB exposure (Table 8). Based on information obtained from the maternal interview and maternal medical records, the list contained data pertaining to demographic background, health history, pregnancy and delivery, obstetrical anesthesia, and exposure to other drugs, such as caffeine, nicotine, and alcohol. Cord blood levels of polybrominated biphenyls (PBBs) were provided by the Michigan Department of Public Health laboratory. Multiple scores were used to verify certain information, e.g., gestational age, perinatal complications, while health-related data were included if they appeared in either source, the medical record or maternal interview. In addition, an Obstetrical Complications Scale (OCS) (Littman & Parmelee, 1974a), modified to omit any items (e.g., infections during pregnancy) which could be consequences of PCB exposure,

Table 8

Potential Confounding Variables

Background

*Socioeconomic status (SES)[a]

Marital status (married/unmarried)

Race

*Maternal age

*Maternal education (years)

*Maternal weight (prior to pregnancy)

*Maternal height

*Maternal body mass[b]

*Sex of infant

*Parity (first born/later born)

*Gravidity (primagravida/multigravida)

Multiple birth[c]

Pregnancy

*Stress (e.g., family illness, marital problems, unemployment)[c]

*Prenatal care (month began)

*Birth class[c]

*Diet (milk and cheese consumed during pregnancy)

Surgery during pregnancy[c]

Exposure to radiation during pregnancy[c]

*Weight gained during pregnancy (net weight gain)

*Weight gained during last 20 weeks of pregnancy (net weight gain)

*Weight loss during pregnancy (total weight lost)

Table 8 (continued)

Reproductive history

- Infertility problems[c]
- Number of previous multiple births (i.e., twins)
- Familial birth defects or anomalies[c]

Delivery

- Cephalopelvic disproportion[c]
- Rh antagonism or other ABO incompatibility[c]
- *Time membranes ruptured (hours prior to delivery)
- *Length of labor (hours)
- *Mode of delivery (spontaneous/Caesarian section)
- *Meconium present in amniotic fluid or meconium staining[c]
- Fetal presentation (vertex/other)
- Abnormal fetal heart-rate during labor[c]
- *Cord around neck[c]
- Placental infarction, placenta previa, or abruptio[c]
- Hypoxia or anoxia[c]
- *Obstetrical complications score (modified)[d]

Drugs during pregnancy

- *Alcohol[e]
- *Caffeine[f]
- *Nicotine (packs of cigarettes per day)
- Marijuana
- Hashish
- Cocaine
- LSD

Table 8 (continued)

Drugs during pregnancy (continued)

- Amphetamines
- Heroin

Drugs prior to pregnancy

- *Alcohol[e]
- *Caffeine[f]
- *Nicotine (packs of cigarettes per day)

Anesthesia and analgesia during labor and delivery

- Meperidine (intramuscular) (mg)
- Meperidine (intravenous) (mg)
- *Vistaril (intramuscular) (mg)
- Vistaril (intravenous) (mg)
- *Carbocaine (pudendal)[c]
- *Xylocaine (pudendal)[c]
- Carbocaine (uterosacral)[c]
- Xylocaine (uterosacral)[c]
- Spinal[c]
- Epidural[c]
- General anesthesia[c]
- Carbocaine (local)[c]
- *Xylocaine (local)[c]
- *Oxytocin (hours)

Polybrominated biphenyl (PBB) (cord serum sample)(ng/mL)

Procedural

1. Infant age at Ballard examination
2. Infant age at NBAS examination

Table 8 (continued)

Note: Items with an asterisk met the criterion that no more than 85 percent of the sample fell in any single category.

[a]Based on Hollingshead index, n.d.

[b]Based on equation: $\frac{\text{weight (kg)}}{\text{height (m)}^{1.5}}$

[c]Recorded as present or absent.

[d]Modified at-risk score based on 24 OCS items which are not likely to be affected by PCBs (e.g., marital status, mode of delivery, chronic illnesses).

[e]Mean daily intake of absolute alcohol (AA) was estimated from the reported rate of consumption of beer, wine, and hard liquor and calculated according to the method described by Kuzma and Kissinger (1981). All servings of a given alcoholic beverage were assumed to be the same size (i.e., 12 oz. for beer, 5 oz. for wine, and 1.25 oz. for hard liquor) and to contain a constant proportion of alcohol by volume (i.e., 0.035 for beer, 0.15 for wine, and 0.45 for hard liquor).

[f]Caffeine consumption was based on a weighted sum of reported consumption of coffee, tea and cola; decaffeinated coffee and herbal tea were not included. It was assumed that the average size of a cup of coffee is about 225 mL. Since previous research has reported that consumption is divided roughly evenly among instant, percolated, and drip coffee (Barr, Streissguth, Martin, & Horst, 1981), the average mg of caffeine per cup of coffee was estimated by taking the mean for instant (74 mg), percolated (74 mg), and drip or filter (112 mg) (Gilbert, Marshman, Schwieder, & Berg, 1976). Since tea and cola contain roughly one third of the average caffeine content of coffee, total daily caffeine consumption was estimated by assigning coffee three times the weight of the other two beverages.

provided a summary score assessing the degree to which the infant was medically at-risk. The modified OCS, based on 24 items relating to maternal age, parity, mode of delivery, drugs, etc., assigns a score to each mother, with higher scores reflecting fewer complications.

Interval scale variables, such as socioeconomic status (SES), maternal age, number of chronic illnesses, amount of caffeine consumed daily, presented no problems for the control analyses. However, to ensure sufficient variance in the case of dichotomous variables, such as marital status (married/unmarried) or parity (first born/later born), only those variables were included for which incidence in each category exceeded 15 percent. Given this criterion, it was possible to assess the effects of 36 potential confounds.

The relation of each potential confounding variable with each independent variable (reported fish consumption or biological measure) was examined in a Pearson product moment correlation analysis. Wherever a potential confound was significantly related

to a given independent variable at an alpha level less than or equal to .10, the confound was held constant in all analyses performed on that independent variable. For each multiple regression analysis we report the results of PCB exposure after the influences of all potential confounds have been partialled out. Similarly, the means reported in the dose-response analyses have been adjusted for the effects of the relevant potential confounds by using analysis of covariance.

Reliability

Staff members were tested for reliability in filling out maternal and infant medical forms with information obtained from the hospital records. Median reliabilities were 90 percent for the maternal and 96 percent for the infant medical records. These estimates are conservative because three examiners had to agree for an item to be counted as an "agreement."

The coding of data into numerical categories was checked by a second coder who recorded all disagreements. These disagreements were then resolved by investigator J. J. After being entered on the computer, data were checked further with a program from the University of Michigan's OSIRIS IV computer package which inspects each variable in the file and flags illegal codes that may have been entered by mistake.

Variable Transformations

Each variable was checked for normality of distribution. Twelve variables were highly positively skewed (skew > 2.0): PCB-fish consumption (highest rate); PCB-fish consumption during

pregnancy; weight loss during pregnancy; time membranes ruptured; length of labor; alcohol, caffeine, and nicotine consumption during pregnancy; alcohol and caffeine consumption prior to pregnancy; oxytocin; and age at NBAS examination. These variables were normalized by means of log transformations. Biological measures of PCB and PBB exposure were also logged in all analyses except those presenting means and standard deviations.

Results

Measures of Exposure

Laboratory results for cord serum, maternal serum, and milk samples are presented in Table 9. The column labeled "nondetectable" refers to PCB values of 0.1 ng/mL to five x the noise level on the chromatogram; the right hand column refers to PCB levels that are detectable, but still below the laboratory's quantification limits. The majority of the PCB levels matched to the 1016 standard were below quantification limits. This was particularly true for the cord and maternal sera analyses. Among these samples, only one of 195 and five of 190 cases, respectively, were quantifiable. Since comparisons with the 1260 standard yielded considerably fewer values below the quantification limit, 1260 values may provide a more reliable measure of PCB body burden. Arithmetic means for the more highly chlorinated isomers exceeded the lower chlorinated isomers by a ratio of 2.7 to 1 for the cord samples and as much as 5.5 to 1 for the neonatal breast milk samples. This differential presumably results from the tendency of lower chlorinated isomers

Table 9

Polychlorinated Biphenyls in Cord Serum,
Maternal Serum, and Maternal Breast Milk (Whole Basis)

	N	Mean (SD)	Median	Nondetectable		Detectable but nonquantifiable	
				N	(%)	N	(%)
Cord serum (ng/mL)							
1016 standard	195	0.9 (0.9)	0.6	23	(11.8)	171	(87.7)
1260 standard	198	2.5 (1.9)	2.0	4	(2.0)	130	(65.7)
Maternal serum (ng/mL)							
1016 standard	190	1.6 (4.5)	0.8	16	(8.4)	169	(88.9)
1260 standard	196	5.5 (3.7)	4.6	0	(0.0)	44	(22.4)
Breast milk - neonatal (ng/g)							
1016 standard	138	4.1 (4.5)	2.9	11	(8.0)	85	(61.6)
1260 standard	138	22.5 (12.3)	20.4	0	(0.0)	2	(1.4)
Breast milk - 5 months (ng/g)							
1016 standard	45	3.7 (3.4)	2.8	3	(6.7)	30	(66.7)
1260 standard	45	17.4 (12.1)	14.1	0	(0.0)	4	(8.9)

Nondetectable refers to values of 0.1 ng/mL to five x noise level of the chromatogram.

Nonquantifiable refers to detectable levels below the quantifiable limits of 5 ng/mL for Aroclor 1016 and 3 ng/mL for Aroclor 1260.

to be less stable, more susceptible to degradation in the environment, and metabolized more rapidly in the organism (Matthews, in press).

PCB levels for a large proportion of the cord serum samples were not quantifiable, even when the 1260 standard was used. A pairwise comparison of PCB 1260 serum levels on a whole basis indicates that mean PCB levels in maternal serum were substantially higher than in cord serum (Table 10), confirming previous findings (Akiyama, Fujitani, Ohi & Yagyu, 1975; Kodama & Ota, 1977). Masuda et al. (1978) found a similar differential in a recent Japanese sample and concluded that the placenta may act as a partial barrier to PCBs. An alternative explanation may be related to the mixture of arterial and venous blood in the cord sample. If lipids and lipophilic substances such as PCBs are retained by the fetus, then arterial blood will contain only residual amounts of these substances, and PCB levels derived from cord serum will under-estimate fetal exposure. Moreover, lipid levels in maternal serum are twice those in cord serum and when PCB concentrations are calculated on a fat basis, the differential is no longer significant. Whichever explanation prevails, the evidence supports the inference that PCBs cross the placenta, thereby exposing the fetus.

Table 10

Pairwise Comparisons of PCBs and Lipids in Cord Serum, Maternal Serum, and Maternal Breast Milk (1260 Standard)

		Whole basis (ng/mL or ng/g)		Fat basis (ng/g)		Lipids	
	N	Mean (SD)	t	Mean (SD)	t	%	t
Cord serum	148	2.4 (1.9)	-10.18*	788.1 (696.5)	-0.82	0.32	-25.69*
Maternal serum		5.3 (3.7)		835.3 (557.1)		0.64	
Cord serum	95	2.4 (1.8)	-15.45*	824.2 (714.2)	0.13	0.31	-20.45*
Breast milk - neonatal		22.8 (13.0)		813.9 (377.9)		2.89	
Maternal serum	91	5.6 (3.2)	-13.36*	932.2 (579.1)	1.55	0.63	-17.06*
Breast milk - neonatal		22.7 (12.3)		827.8 (380.4)		2.85	
Breast milk - neonatal	42	20.0 (9.3)	1.31	750.5 (408.8)	-0.19	2.96	0.51
Breast milk - 5 month		18.0 (12.2)		772.3 (671.2)		2.82	

Cord and maternal sera values on a whole basis are given in ng/mL and breast milk values in ng/g.

*$p < .0001$

PCB values were also obtained for two samples of breast milk, one during the first few weeks after birth and a more limited sample when the infant was 5 months old. Matched pair *t*-tests indicate that PCB levels on a whole basis were substantially higher in breast milk than cord and maternal sera samples. Again, when samples were compared on a fat basis, differences were no longer significant. Kodama and Ota (1980) suggested that breast-feeding may decrease PCB body burden in the mother. Although PCB concentrations in the breast milk of nursing mothers in our sample tended to decline over time, this decline was not significant.

Correlations among PCB levels in the four biological specimens are shown in Table 11. The highly significant correlation of cord with maternal serum levels provides further evidence for the transplacental passage of the PCB molecule and corroborates a similar relation reported by Masuda et al. (1978) and Kodama and Ota (1977), using smaller samples of women. The significant correlation between PCBs in maternal serum and breast milk indicates that PCBs are moderately stable in the mother, an inference further supported by the significant correlations between breast milk samples obtained shortly after the baby's birth and those obtained at 5 months.

Table 11

Intercorrelations of Log PCBs (1260 Standard)
in Cord Serum, Maternal Serum, and Maternal Breast Milk

	Cord serum	Maternal serum	Breast milk neonatal	Breast milk 5-month
Cord serum	--	.41*** (148)	.09 (95)	-.06 (25)
Maternal serum	.43*** (145)	--	.23* (91)	.01 (30)
Breast milk - neonatal	.16 (93)	.28** (91)	--	.61*** (42)
Breast milk - 5 month	-.01 (24)	-.10 (30)	.30* (42)	--

Note. Rs above the main diagonal are values calculated on a whole basis, while those below are on a fat basis. N appears in parentheses. Lipid values were missing for three cord serum, two neonatal breast milk, and one 5-month breast milk samples.

*$p < .05$

**$p < .01$

***$p < .0001$

Correlations between maternal and cord sera were similar in magnitude, whether calculated on a whole serum or fat basis, r = .41 and .43, respectively (Table 11). While the whole and fat basis findings were also similar for correlations between maternal serum and breast milk, the two approaches yielded different results for the neonatal to 5-month breast milk correlation.

Consistency between analyses derived on a whole and fat basis was also indicated by the pattern of the intercorrelations shown in Table 12. PCB levels in the cord and maternal sera on a whole serum basis were highly correlated with levels calculated on a fat basis (r = .93). Thus, for serum, it seems to make little difference whether measures are derived on a whole or fat basis. Although cord and maternal sera are low in lipids, lipid levels tend to be relatively stable. Because breast milk lipids fluctuate considerably, the same consistency does not appear for breast milk values derived by the two methods. This apparent instability suggests that in the analyses of breast milk, measures that take lipid fluctuation into account are likely to be more reliable.

Table 12

Intercorrelations of Log PCBs (1260 Standard)
in Cord Serum, Maternal Serum,
and Maternal Breast Milk
(Whole and Fat Basis)

	Whole basis			
	Cord serum	Maternal serum	Breast milk-neonatal	Breast milk-5 month
Fat basis				
Cord serum	.93*** (194)	.37*** (145)	.07 (93)	.05 (24)
Maternal serum	.43*** (148)	.93*** (196)	.20+ (91)	.01 (30)
Breast milk-neonatal	.16 (95)	.35*** (91)	.62*** (138)	.30* (42)
Breast milk-5 month	-.06 (25)	-.08 (30)	.08 (42)	.39** (45)

Note. N appears in parentheses.

+p < .10

*p < .05

**p < .01

***p < .001

These findings were further supported by an analysis of the degree to which PCB levels could be predicted from lipid levels in serum or breast milk. While the PCB levels in the cord and maternal sera were unrelated to corresponding cord and maternal lipid levels, there was a significant association between PCB and lipid levels in the neonatal and 5-month breast milk (r = .58, p < .0001, and r = .63, p < .0001, respectively).

Women and their offspring were selected for the study on the basis of reported fish consumption patterns. Levels of fish consumption reported by the exposed and control mothers for whom the different biological measures were available are shown in Table 13. When women who breast-fed were compared with those who did not, no difference was found for highest annual rate or cumulative consumption measures. While their rate during pregnancy was slightly lower than the rest of the sample (M = 2.9 vs. 3.8 PCB-kg/year), the difference failed to reach conventional levels of statistical significance (t =1.90, p < .10).

Correlations between maternal reports of contaminated fish consumption and the four biological measures of PCB body burden are presented in Table 14. No relationship was found between cord serum PCB levels and maternal fish consumption, possibly

Table 13

Levels of Reported Contaminated Fish Consumption (PCB-kg)
of Women Providing Blood and Breast Milk Samples

	N	Mean	(SD)	Median	Range
Cord serum analyses					
Consumption at highest rate	198	4.3	(5.5)	3.0	0.0 - 41.7
Consumption during pregnancy	189	2.8	(3.9)	1.9	0.0 - 22.4
Cumulative consumption	198	61.3	(97.8)	27.8	0.0 - 716.6
Maternal serum analyses					
Consumption at highest rate	196	4.4	(5.5)	3.2	0.0 - 41.7
Consumption during pregnancy	190	2.8	(3.6)	2.2	0.0 - 22.4
Cumulative consumption	196	62.4	(97.5)	28.6	0.0 - 716.6
Breast milk - neonatal					
Consumption at highest rate	138	4.7	(5.3)	3.3	0.0 - 41.7
Consumption during pregnancy	135	2.9	(3.5)	2.2	0.0 - 20.0
Cumulative consumption	138	62.9	(90.9)	38.4	0.0 - 716.6
Breast milk - 5 months					
Consumption at highest rate	45	5.5	(8.0)	3.8	0.0 - 41.7
Consumption during pregnancy	45	2.8	(2.9)	2.2	0.0 - 9.5
Cumulative consumption	45	82.5	(135.3)	43.4	0.0 - 716.6

Note. Mean consumption levels include data on exposed and control women.

because of the detection problems in cord serum analysis described earlier. In contrast, a positive correlation was found between PCB levels in maternal serum and all three reported fish consumption measures. Mean PCB level in maternal serum was 6.1 ng/mL (*SD* = 3.7) among women who ate contaminated fish, as contrasted to 4.1 ng/mL (*SD* = 2.7) among those who abstained (*t* = 3.83, *p* < .0001). These data replicate in a sample of women of child-bearing age Humphrey's (1976) finding that Lake Michigan fish consumption predicts PCB body burden in Michigan residents. The data extend this finding by showing a significant correlation between fish consumption and PCB levels in neonatal breast milk. Mean PCB residues were higher in breast milk samples of exposed than in samples of nonexposed women (*M* = 865.6 vs. 622.2 ng/g on a fat basis, *t* = 3.21, *p* < .005). The lack of a consistent relationship between maternal report obtained at birth and breast milk levels at 5 months may be due in part to postpartum ingestion of contaminated fish, which will be examined in future analyses. Figure 2 shows a scatterplot demonstrating the linear relationships between maternal serum 1260 and fish consumption at the highest annual rate. For every pound of contaminated fish ingested by the mother, the PCBs in her serum increase by about 0.15 ng/mL on a whole basis or 23.6 ng/g on a fat basis.

Table 14

Correlations between Log Contaminated Fish Consumption and Log PCBs in Cord Serum, Maternal Serum, and Breast Milk (1260 Standard)

	N	r	Regression equation
Fish consumption at highest annual rate with			
Cord (whole serum basis)	198	.09	y = 1.05 + .04x
Maternal (whole serum basis)	196	.38***	y = 1.47 + .15x
Breast milk - neonatal (fat basis)	138	.30***	y = 6.36 + .12x
Breast milk - 5 month (fat basis)	45	.24	y = 6.24 + .11x
Fish consumption during pregnancy with			
Cord (whole serum basis)	189	.13	y = 1.05 + .05x
Maternal (whole serum basis)	190	.31***	y = 1.57 + .13x
Breast milk - neonatal (fat basis)	135	.24**	y = 6.47 + .10x
Breast milk - 5 month (fat basis)	45	.36*	y = 6.19 + .18x
Cumulative fish consumption (normalized) with			
Cord (whole serum basis)	198	.08	y = 1.05 + .02x
Maternal (whole serum basis)	196	.29***	y = 1.52 + .07x
Breast milk - neonatal (fat basis)	138	.21**	y = 6.38 + .06x
Breast milk - 5 month (fat basis)	45	.10	y = 6.31 + .04x

*$p < .05$

**$p < .01$

***$p < .001$

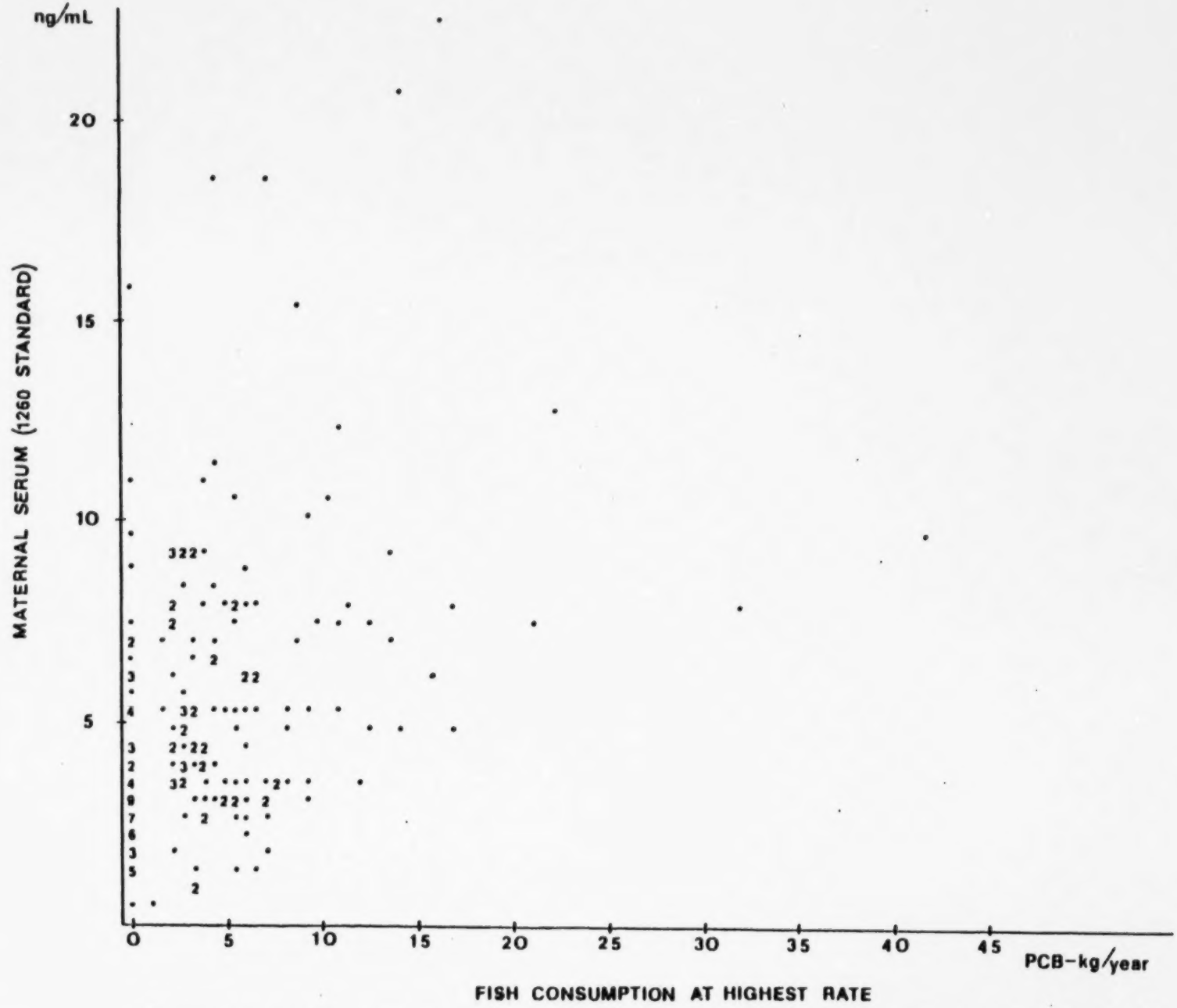


Figure 2. Scatter plot of maternal serum (1260 standard) by fish consumption at highest rate.

Infant Outcomes

Infant outcomes were examined for two measures of exposure--reported maternal PCB-fish consumption at the highest rate and cord serum PCB level (1260 standard). As the best predictor of maternal serum and breast milk PCBs, fish consumption at the highest rate may provide a useful estimate of intrauterine exposure. Although PCB levels in cord serum are a more direct measure of infant exposure, most values are below the quantification limit and, therefore, this measure may lack the reliability needed to detect subtle effects. Since toxins other than PCBs are also found in Lake Michigan fish, however, cord serum was used to corroborate findings obtained from the analyses of maternal fish consumption.

Table 15 presents the correlations of 36 potential confounding variables with each of these exposure measures, indicating those at an alpha level less than or equal to .10. Maternal PCB-fish consumption is correlated with caffeine consumption before and during pregnancy and with alcohol consumption before and during pregnancy. Cord serum PCB level is associated with alcohol and caffeine consumption during pregnancy, weight gain during pregnancy, and maternal age. Polybrominated biphenyls (PBBs), a chemically related compound which entered the Michigan food chain through the accidental contamination of cattle feed, is not correlated with either measure of PCB exposure. Serum PBB levels are consistently low in this sample, $\underline{M}$ = 0.4 ng/mL, $\underline{SD}$ = 0.7. Since eight correlations at the $\underline{p} < .10$ significance level is about what would be predicted by chance, it seems unlikely that the correlations in Table 15 will replicate beyong the present sample. It is necessary to control for these potential confounds in the present analyses, however, in

Table 15

Correlations of PCB Exposure Measures

with Potential Confounding Variables

	PCB-fish consumption (highest rate)	Cord serum PCB level
Background		
Socioeconomic status	-.08	.07
Maternal age	.01	.12+
Maternal education	-.05	.01
Maternal weight	-.09	.11
Maternal height	-.02	.06
Maternal body mass	-.08	.09
Sex of infant	.07	-.07
Parity	.02	.04
Gravidity	.09	-.01
Pregnancy		
Stress	-.01	-.05
Prenatal care	-.05	-.02
Birth class	-.00	-.04
Diet	.04	-.01
Weight gain (total)	-.03	-.14+
Weight gain (last 20 weeks)	.06	-.09
Weight loss	.01	.08

Table 15 (continued)

	PCB-fish consumption (highest rate)	Cord serum PCB level
Delivery		
Time membranes ruptured	-.04	-.08
Length of labor (hours)	-.04	-.01
Mode of delivery	.02	-.04
Meconium	-.00	-.09
Cord around neck	-.05	-.00
Obstetrical complications	-.06	-.04
Drugs during pregnancy		
Alcohol	.14*	.14+
Caffeine	.10+	.12+
Nicotine	.04	.09
Drugs prior to pregnancy		
Alcohol	.17**	.10
Caffeine	.12*	.02
Nicotine	.02	.11
Anesthesia and analgesia		
Vistaril (intramuscular)	-.01	.09
Carbocaine pudendal	-.06	.01
Xylocaine pudendal	-.00	.02
Xylocaine local	-.08	.05
Oxytocin	.03	-.06

Table 15 (continued)

	PCB-fish consumption (highest rate)	Cord serum PCB level
Polybrominated biphenyls (PBBs)	.08	.04
Procedure		
Age at Ballard examination	-.03	-.00
Age at NBAS examination	.09	-.02

Note: More detailed definitions of these variables are presented in Table 8.

+ $p \leq .10$

* $p < .05$

** $p < .01$

order to insure that PCB effects found in the present sample are not attributable to these related variables.

Effects on Birth Size and Gestational Age

The relation between maternal PCB-fish consumption and birth size is shown in Table 16. The *F*-ratios test the statistical significance of each predictor after the effects of the other four predictors have been partialled out. Two measures of newborn size--birth weight and head circumference--are significantly correlated with maternal PCB-fish consumption, with higher levels of contaminated fish consumption predicting smaller birth size.

In order to examine dose-response relationships, PCB-fish consumption was divided into four categories. Mothers who reported having eaten Lake Michigan fish were divided into three approximately equal-sized groups: (a) high exposure (greater than 6.5 kg per year); (b) moderate exposure (3.5-6.5 kg); and (c) low exposure (1.9-3.4 kg). The fourth group consisted of mothers who did not eat Lake Michigan fish. Birth weight decreases in a dose-related fashion at each level of additional PCB exposure (Figure 3). Even after adjusting for the effects of the four potential confounds, the birth weight of the most highly exposed infants averages 245 g less than that of the nonexposed controls. Head circumference also decreases in a dose-

Table 16

Maternal Contaminated Fish Consumption and Cord Serum PCB Level: Effects on Birth Size and Gestational Age

	Birth Weight		Head Circumference		Gestational Age[a]		Ballard	
	β[b]	F[c]	β[b]	F[c]	β[b]	F[c]	β[b]	F[c]
Contaminated Fish Consumption								
Controlling for potential confounds								
Contaminated fish consumption	-.21	13.01***	-.20	10.67**	-.15	5.67*	-.30	16.05***
Alcohol prior to pregnancy	.05	<1	.15	4.91*	.06	1.38	.06	<1
Alcohol during pregnancy	.01	<1	-.05	<1	-.06	<1	-.14	2.20
Caffeine prior to pregnancy	-.13	3.17	-.07	<1	-.14	3.04	.14	2.24
Caffeine during pregnancy	.02	<1	-.02	<1	.11	2.37	-.05	<1
Controlling for gestational age[a] and potential confounds[d]								
Contaminated fish consumption	-.16	7.69*	-.19	7.97*				
Cord Serum PCB Level								
Controlling for potential confounds								
Cord serum PCB level	-.16	5.25*	-.18	6.53*	-.19	5.16*	-.07	<1
Alcohol during pregnancy	.03	<1	.04	<1	-.07	<1	.11	<1
Caffeine during pregnancy	-.04	<1	.01	<1	.09	1.27	.03	<1

Table 16 (continued)

	Birth Weight		Head Circumference		Gestational Age[a]		Ballard	
	β[b]	F[c]	β[b]	F[c]	β[b]	F[c]	β[b]	F[c]
Controlling for potential confounds (continued)								
Weight gain during pregnancy	.23	11.11**	.16	5.30*	.12	1.98	.04	<1
Mother's age	.03	<1	.02	<1	-.02	<1	-.14	1.47
Mother's prepregnancy weight	.27	15.18***	.15	4.85*	.12	2.06	.07	<1
Sex of infant	-.14	4.21*	-.36	26.51***	.04	<1	-.08	<1
Controlling for gestational age[a] and potential confounds[d]								
Cord serum PCB level	-.09	1.73	-.15	3.86				

[a]Based on reported last menstrual period.

[b]Standardized regression coefficient from the final step of the regression.

[c]Tests the unique variance associated with each predictor, i.e., the degree to which the predictor adds significantly to the explained variance when entered last in the regression.

[d]Regression coefficients for the potential confounds in this analysis are available on request.

*$p < .05$

**$p < .01$

***$p < .001$

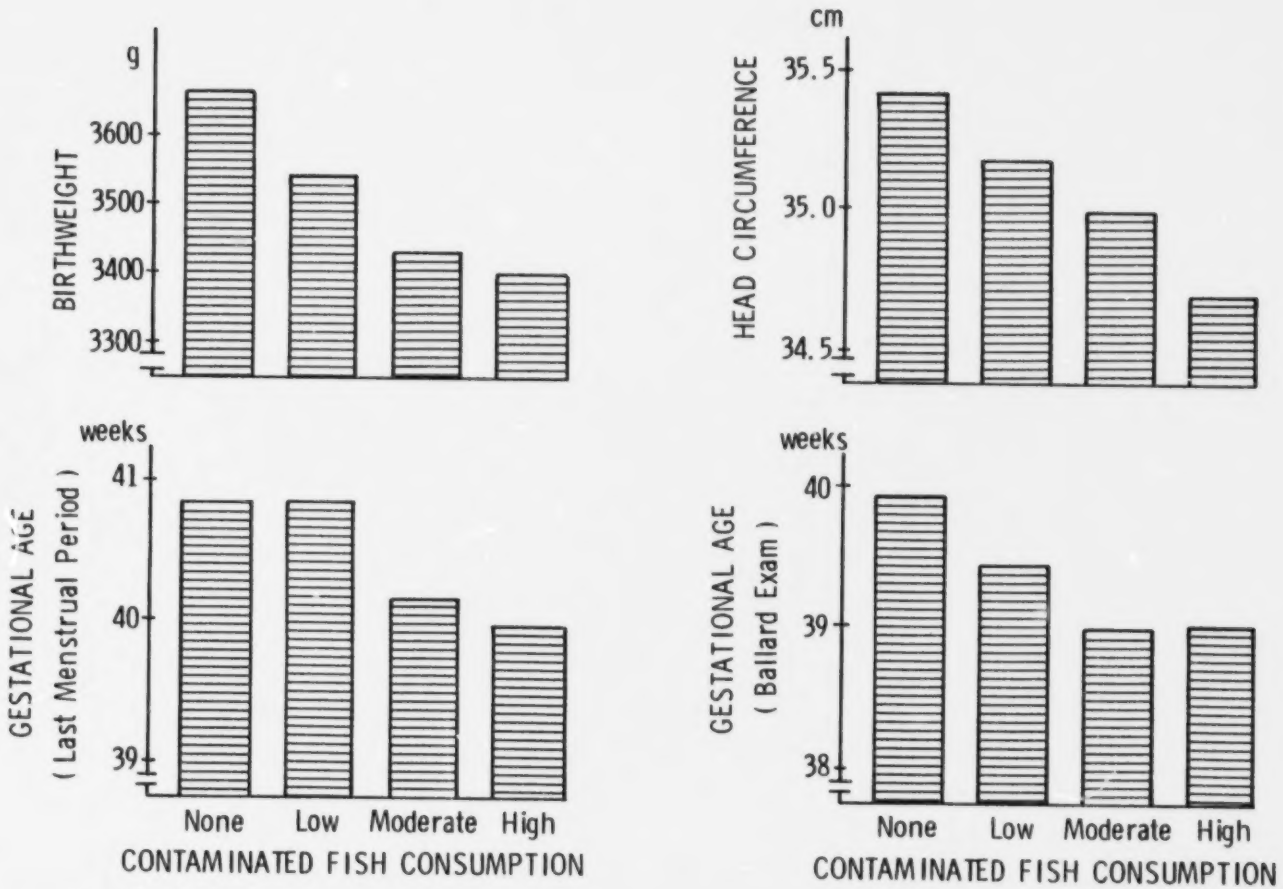


Figure 3. Dose-response relationships for birth size and gestational age by level of contaminated fish consumption. Based on analyses of co-variance in which the means for each group were adjusted for the effects of caffeine and alcohol consumption before and during pregnancy. Exposure groups are as follows: high = 6.6 - 41.7 kg/year ($\underline{n}$ = 78); moderate = 3.5 - 6.5 kg/year ($\underline{n}$ = 82); low = 1.9 - 3.4 kg/year ($\underline{n}$ = 81).

related fashion, with the head circumference of the most highly exposed infants averaging 0.7 cm less than the controls. Head circumference is not disproportionately small, given the low weight of these infants. With birth weight held constant, the effect of fish consumption on head circumference drops below conventional levels of significance, F (1, 272) = 2.92, $p > .05$.

Contaminated fish consumption also predicts a shorter gestational period on both the last menstrual period measure and the Ballard examination (Table 16). Greater exposure is associated with greater immaturity on both subscales of the Ballard examination: F (1, 167) = 10.67, $p < .001$ for neuromuscular maturity; F (1, 164) = 8.44, $p < .01$ for physical maturity. Gestational age decreases in a dose-related fashion, with the most highly exposed infants averaging gestational periods that are 6.3 days shorter than the nonexposed controls on both gestational age measures (Figure 3).

Since birth weight and gestational age are moderately intercorrelated (r = .36 and .46 for the last menstrual period and Ballard measures, respectively), it is possible that the effects shown in Table 16 are not independent. For example, the smaller birth size found to be associated with PCB exposure could actually be a consequence of the exposed infants' earlier birth. Conversely, the apparent immaturity indicated by the Ballard examination may merely be a by-product of the infants' smaller birth size. These hypotheses were tested in multiple regression analyses in which the effect of fish consumption on each of these variables was examined after controlling

for the effects of the others. With gestational age based on last menstrual period statistically controlled, fish consumption continues to predict both lower birth weight and smaller head circumference (Table 16), indicating that the affected infants are smaller-for-date. Fish consumption also predicts lower Ballard scores when birth size is held constant, F (1, 203) = 4.96, $p < .05$, suggesting that the exposed infants' poorer Ballard scores are not attributable to their smaller size.

Because contaminants other than PCBs could be responsible for the observed relations between fish consumption and birth size or gestational age, we attempted to corroborate the findings in Table 16 using the cord serum PCB measure (1260 standard). Two variables, maternal prepregnancy weight and sex of infant, were found to function as suppressor variables in the present sample due to a tendency for cord PCB levels to be higher in the offspring of heavier mothers and in male infants. Since the infants of heavier mothers tend to be larger (r = .24, $p < .001$, and r = .13, $p < .10$, with birth weight and head circumference, respectively) and since male infants tend to be larger than female infants (t (192) = 2.34, $p < .025$, and t (192) = 5.31, $p < .001$, for birth weight and head circumference, respectively), these variables initially masked the effect of cord PCB level on birth size. With maternal prepregnancy weight, sex of infant, and four potential confounding variables statistically controlled, cord serum PCB level predicts lower birth weight, smaller head circumference, and a shorter period of gestation based on reported last menstrual period (Table 16). Infants with cord serum levels greater than 5 ng/mL are 194 g lighter on the average when compared with infants whose levels are below the laboratory's

quantification limit (3 ng/mL). The head circumference of the more highly exposed infants averages 0.3 cm less, and they are born on an average of 13.3 days earlier.

Effects on Neonatal Behavior

In order to assess the overall impact of PCB exposure on neonatal behavior, PCB-fish consumption (adjusted for the effects of four potential confounds) was examined in relation to the NBAS clusters. Fish consumption was adjusted in the following manner. First, it was regressed on its four potential confounding variables. The regression coefficients from that analysis were then used to calculate a predicted fish consumption score for each mother, given her scores on the confounding variables. The predicted score was subtracted from her actual score in order to remove the variance attributable to the confounds. This adjusted score was then regressed on six of the NBAS clusters. The seventh cluster, response decrement, was omitted due to a large number of missing observations.

PCB-fish consumption (adjusted for the four potential confounds) predicts a linear combination of five NBAS clusters, F (5, 193) = 3.18, $p < .01$, with a multiple correlation coefficient (R) of .28 (see Table 17). The strongest relationships are with autonomic maturity, reflexes, and range of state. Each of the items in the autonomic and range of state clusters was examined in a separate regression analysis similar to those in Table 16. PCB-fish consumption predicts two of the three autonomic items: motor maturity, F (1, 280) = 6.93, $p < .01$; and amount of startle, F (1, 280) = 10.07, $p < .005$; and one of the four range of state items: lability of states, F (1, 279) = 14.46, $p < .001$. Motoric immaturity (Scale points 1, 2,

Table 17

Maternal PCB-Fish Consumption: Effects on Neonatal Behavior

	Raw regression coefficient	Standardized regression coefficient	F
Autonomic maturity	-0.2	-.17	5.85**
Reflexes	0.1	.14	3.97*
Range of state	-0.2	-.14	3.65+
Orientation	-0.0	-.06	<1
Regulation of state	-0.0	-.04	<1
Tonicity[a]			
Constant	1.7		

Note: Based on a multiple regression analysis in which fish consumption (adjusted for the effects of caffeine consumption before and during pregnancy and alcohol consumption before and during pregnancy) was regressed on six NBAS clusters.

[a] *F*-to-enter at the last step was too small to permit entry into the regression.

+ $p < .07$

* $p < .05$

** $p < .025$

and 3) is defined as jerky, unbalanced, cogwheel-like movement in which flexor and extensor muscles seem to be competing. Eleven percent of the highly exposed infants are classified as immature in this sense, as compared with only 3% of the nonexposed controls. It has been suggested that fewer than six state changes during the NBAS examination indicates deficient lability of state (Als et al., 1979, Table 6-1). Given this criterion, 42% of the highly exposed infants are hyporesponsive compared with only 17% of the nonexposed controls.

The 17 reflex items were not examined individually. Although the reflex cluster exhibits moderate internal consistency reliability (J. Jacobson et al., in press), individual items administered in a single examination are not likely to be reliable. The reflex items were therefore factor analyzed in order to assess whether particular subgroups of reflexes might be influenced by PCB exposure. Three factors each account for at least 10% of the variance in the reflex cluster scores: (a) reflexes associated with the legs: standing, walking, placing; (b) reflexes associated with the mouth: rooting, sucking; and (c) a third group consisting of Babinski, passive movements, and tonic deviation. PCB-fish consumption is related to only one of these subgroups: reflexes associated with the mouth, $\underline{F}$ (1, 281) = 7.22, $\underline{p} < .01$. A second analysis differentiated reflexes which are abnormally strong or hyperactive from those which are abnormally weak or difficult to elicit. PCB-fish consumption is significantly related to number of abnormally weak reflexes, $\underline{F}$ (1, 281) = 9.63, $\underline{p} < .005$.

Als et al. (1979) have proposed a set of a priori clusters which classify neonatal behavioral performance qualitatively as being either optimal, normal, or worrisome. The "worrisome" category describes a behavioral pattern that is sufficiently deviant to warrant the concern of the experienced clinician. The Als et al. criteria for classifying each of the NBAS items (1979, Table 6-1) were applied to the seven clusters used in the present study.[11] As indicated in Table 18, maternal fish consumption is highest among infants classified as worrisome on the three clusters associated with PCB exposure. On the range of state cluster, where two categories of worrisome behavior are defined, exposure is highest among the infants classified as flat or depressed. Tables 19-21 compare the most highly exposed infants with the non-exposed controls. High levels of contaminated fish consumption increase the likelihood of worrisome performance on all three clusters.

Since small birth size and shortened gestation may themselves be associated with neonatal behavioral deficits, it is possible that the behavioral effects found here are not direct consequences of exposure to PCB but merely by-products of PCB effects on birth size and gestational age. This hypothesis implies that, when birth size and gestational age are statistically controlled, the effect of exposure on behavioral outcome will no longer be significant (Kenny, 1979). Partial correlation analyses (Table 22) indicate that the behavioral effects of contaminated fish consumption are not

Table 18

Maternal PCB-fish Consumption (kg/yr.) for Infants Classified as "Worrisome" on Three NBAS Clusters

				Worrisome		
	Optimal	Normal	Worrisome	Excessively labile	Flat, depressed	F
Autonomic maturity	--[a]	5.0 (277)	9.3 (10)			4.88*
Reflexes	3.7 (47)	4.7 (175)	7.7 (65)			8.07**
Range of state	5.6 (95)	4.5 (159)	--[b]	2.9 (12)	10.4 (20)	7.02**

Note: N's are given in parentheses.

[a]No optimal criteria are designated by Als et al. (1979) for autonomic maturity.

[b]Two categories of worrisome behavior are defined for range of state.

* $p < .05$

** $p < .001$

Table 19

Worrisome Performance on the Autonomic Maturity

Cluster by PCB-fish Consumption

	Nonexposed controls	High exposure (>6.5 kg/yr.)
Normal	64	67
Worrisome	1	6

χ^2 (1) = 3.18, p <.08

Table 20

Worrisome Performance on the Reflex Cluster

by PCB-fish Consumption

	Nonexposed controls	High exposure (>6.5 kg/yr.)
Optimal or normal	44	35
Worrisome	21	38

χ^2 (1) = 5.48, p <.025

Table 21

Worrisome Performance (Flat, Depressed) on the Range of State Cluster by PCB-fish Consumption

	Nonexposed controls	High exposure (>6.5 kg/yr.)
Optimal, normal, or excessively labile	64	65
Worrisome (flat, depressed)	1	7

χ^2 (1) = 4.16, p <.05

Table 22

Partial Correlations of Adjusted Contaminated Fish Consumption with Neonatal Behavior, Controlling for Birth Size and Gestational Age

Behavioral outcome	Zero-order relationship (N=287)	Control Variable: Birth weight (N=282)	Head circumference (N=272)	Gestational age[a] (N=226)	Ballard score (N=121)
Autonomic maturity	-.16**	-.16**	-.17**	-.15*	-.09
Reflexes	.17**	.16**	.16**	.17**	.15
Range of state	-.09	-.08	-.08	-.09	-.09
Lability of states	-.23***	-.21***	-.23***	-.24***	-.23***

[a]Based on reported last menstrual period

*$p < .05$

**$p < .01$

***$p < .001$

predicted by either birth size or gestational age based on last menstrual period. Controlling for the size and gestational age of the newborn does not appreciably alter the relation of contaminated fish consumption to NBAS performance.

The pattern is less clear for the Ballard examination. Although controlling for the Ballard has little effect on the relation of contaminated fish consumption with lability of states or reflexes, the effect on autonomic maturity is substantially reduced when the Ballard is held constant (Table 22). Nevertheless, it does not seem appropriate to conclude that this effect is mediated by shortened gestation. Unlike gestational age based on last menstrual period, it is possible that the Ballard scores are themselves influenced by neonatal behavioral deficits. Ballard et al. (1979) note that certain disease states and intrauterine environmental factors may retard physical and neurological maturation, thereby causing affected infants to appear gestationally younger than they are. Thus, the newborn who exhibits motoric immaturity or a propensity to startle is likely to be scored behaviorally or physically younger on the Ballard exam. The partial correlation analysis should, therefore, not be interpreted as evidence that gestational age mediates these behavioral outcomes, since low Ballard scores and poor autonomic functioning may both be due to neurobehavioral immaturity resulting from toxic exposure.

Evidence that the physical and behavioral effects of PCBs are independent suggests that some affected infants are small while others exhibit only behavioral deficits. The total impact of PCB exposure in the present sample can be estimated most completely by examining the relation between adjusted fish consumption and a linear combination of birth size, gestational age, and behavioral variables. The multiple correlation between fish consumption and neonatal outcome emerging from this analysis is .34, F (7, 152) = 2.80, $p < .01$.

An attempt was made to corroborate the behavioral effects associated with maternal PCB-fish consumption in analyses based on the cord serum measure. Serum PCB level (adjusted for its four potential confounds) is not significantly correlated either with a linear combination of six NBAS clusters, F (5, 118) = 1.13, or with any of the individual clusters. Further examination of the data did not reveal any control variables that might be suppressing the relation between cord serum PCB levels and neonatal behavior.

Discussion

Measures of Exposure

Despite their widespread distribution in our environment and concern about human accumulation, few studies are currently available on the serum PCB levels of individuals chronically exposed to PCBs via their diet. Moreover, the toxicology of PCBs is little understood in comparison with that of other xenobiotic chemicals, such as DDT and BHC (Hirayama, 1976; Yoshimura & Yoshimura, 1976). The present longitudinal study was designed to investigate effects of PCB exposure from contaminated fish consumption on two potential at-risk groups, pregnant women and their newborn offspring. While several

reports have appeared on the transfer of PCBs from mother to child via breast milk (e.g., Kodama & Ota, 1980; Kuwabara, Yakoshiji, Watanabe, Yoshida, Koyama & Kunita, 1979), only a few studies examined the transfer of PCBs *in utero* (Akiyama et al., 1975; Kodama & Ota, 1980; Masuda et al., 1978). These studies used either relatively small unexposed samples or women and infants exposed during the *Yusho* incident. No study to date has examined the pattern of transfer from mothers to offspring exposed via the food chain.

The data in this report provide empirical support for linkages between source of contamination and body burden shown in the analytic model (Figure 1). They also provide evidence of the proponderance of more heavily chlorinated isomers in the serum and breast milk of women whose exposure to PCBs is due in part to the ingestion of contaminated fish. The small amounts of 1016 present in the biological specimens and the poor reliability of their measurement indicates that values matched to the 1260 standard are more likely to yield meaningful findings.

The present study evaluated the linkages from fish consumption to maternal body burden and subsequently to the developing fetus and breast milk. Even though exposure levels are only moderate in the women studied, reported contaminated fish consumption predicts PCB residues in two measures of body burden, maternal serum and breast milk. These results confirm prior studies which found an association between fish consumption and PCB residues in serum specimens (Kreiss et al., 1981; Humphrey, 1976), while also demonstrating that the relationship holds for younger women, an age group not previously studied. The particular significance of this finding is that PCBs in the environment may pose a risk to the fetus and newborn, since the women in this age group are in the middle of their child-bearing years.

Transplacental passage by the PCB molecule was indicated by the significant positive correlation between maternal and cord sera (r = .41, p < .0001), confirming two prior studies which yielded similar findings (r = .24, Masuda et al., 1978; r = .45, Kodama & Ota, 1977). The transfer of PCBs to breast milk was confirmed by a similar positive correlation (r = .27, p < .01, for maternal serum on a whole basis to neonatal breast milk on a fat basis), confirming Masuda et al.'s finding (r = .29, 1978). While cord and maternal sera yield similar results regardless of whether the analysis is performed on a whole serum or fat basis, breast milk residues yield varying results due presumably to fluctuations in lipid levels in breast milk.

The present data are consistent with the notion that PCBs move through the environment and the human body into systems which may potentially threaten the infant both before and after birth (Swain, 1981). At this time it is not clear which of these exposures--prenatal (intrauterine) or post-natal (via breast milk)--has the greater impact on infant development. While the absolute quantity of PCB residues is substantially lower in cord serum than in breast milk, the fetal organism is particularly vulnerable during the prenatal period. One factor overlooked in this debate (e.g., Masuda et al., 1978) is the size of the fetus. When PCB-exposure is calculated on the basis of body weight, the infant's prenatal exposure is substantial. In addition, the values for PCBs in cord serum may underestimate actual levels of exposure for reasons discussed earlier. Moreover, different biological systems in the fetus and newborn may be affected depending on the developmental period during which exposure occurs.

Methodological Considerations

As measures of intrauterine exposure, reported contaminated fish consumption and cord serum PCB levels each have disadvantages. Since toxic chemicals other than PCBs are also found in Lake Michigan fish, the association of fish consumption with adverse neonatal outcomes needs to be corroborated by a more direct measure of PCB body burden. However, at the moderate exposure levels examined in the present study, the majority of cord serum samples yield PCB values below the laboratory's qualification limit. Given the uncertain reliability of the cord serum measure, reported fish consumption may provide a more accurate measure for moderately-exposed infants. It may also provide a better measure of chronic exposure, since cord serum is sampled only at birth.

Since ethical considerations do not permit the random assignment of humans to experimental conditions, the present study used a correlational design. Thirty-five potential confounding variables were tested for an association with fish consumption and cord serum PCBs. In the analysis of infant outcomes, variables with p values $<.10$ were controlled using either multiple regression or analysis of covariance. Other potential confounds, such as socioeconomic status, maternal smoking, parity, obstetrical complications, and exposure to PBBs are unrelated to maternal fish consumption and cord serum PCB levels. These variables, therefore, cannot account for the adverse neonatal outcomes associated with PCB exposure. With relevant confounding variables controlled, maternal fish consumption predicts adverse outcomes in three areas: birth size, gestational age, and neonatal behavior.

Birth Size and Gestational Age

Intrauterine exposure to PCBs is most clearly associated with reduced birth size and a shorter period of gestation. The most highly exposed infants in this sample are about 200-250 g lighter than the nonexposed controls, whether exposure is measured by maternal fish consumption or cord serum PCB levels. Similar effects hold for head circumference and gestational age based on reported last menstrual period. All three measures decrease in a dose-related fashion with increasing levels of PCB exposure. Evidence of reduced birth size and shortened gestation in this chronically-exposed sample is consistent with research on acutely-exposed humans in Japan (Funatsu et al., 1972) and with experimental studies using rhesus monkeys (Allen et al., 1980).

The birth weight effect found here is of the same order of magnitude reported by the Surgeon General (1979) for smoking during pregnancy; the infants of smokers are on the average 200 g lighter than those of nonsmokers. In contrast to smoking, however, there is no evidence that abstaining from fish consumption during pregnancy will reduce this effect, since PCBs (especially the more highly chlorinated isomers that are matched to the 1260 standard) accumulate in human tissue over time and are difficult to eliminate.

Neonatal Behavior

PCB-fish consumption also predicts neonatal behavioral deficits, including (a) autonomic immaturity, as indicated by a greater propensity to startle and poorer motoric, reflex, and neuromuscular functioning; and (b) depressed responsiveness, as indicated by a greater number of hypoactive

reflexes and more limited lability of state. Analyses based on the Als et al. (1979) criteria suggest that these behavioral effects are of sufficient magnitude to warrant the concern of the experienced clinician. These findings are consistent with reports of depressed reflexes and sluggishness in the animal literature (Storm et al., 1981; Tilson et al., 1979) and with Japanese reports of sluggish, clumsy, and jerky movement, apathy, and hypotonia in somewhat older acutely exposed human infants (Harada, 1976). Because the chronic low level exposure in the present population is not associated with chloracne and other rashes that mark the Yusho syndrome, these neonatal behavioral deficits are less likely to be noticed, and behavioral disturbances emerging later in development are less likely to be traced to intrauterine PCB exposure.

The association of contaminated fish consumption with neonatal behavioral deficits is not corroborated by the cord serum measure of PCB exposure. This discrepancy may be due, in part, to the poor reliability of the cord serum measure. In addition, cord samples were available for only 48.7% of the infants with the highest fish consumption exposure levels (> 10 kg/yr.), compared with 65.3% for the remainder of the sample, so that the range of exposure levels available for the cord PCB analyses is more restricted. Alternatively, it is possible that the behavioral deficits associated with fish consumption are due to toxins other than PCBs that are present in the same contaminated fish. Toxaphene, for example, has recently been detected in fatty Lake Michigan fish in quantities comparable to those of PCBs (Everett, 1982).

According to Spyker's (1975) model, a toxin may be associated with morphological, maturational, reproductive, or behavioral disorders. The symptoms exhibited by a particilar individual depend on such variables as genetic predisposition, period of development when exposed, and when the assessment is made. Spyker suggests that at high levels of exposure a toxin may be sufficiently potent to produce a coherent syndrome of effects, but at lower levels individuals are likely to exhibit disparate symptoms. The case of PCBs confirms these predictions. Path analytic models show that the birth size and behavioral effects are largely independent in the present sample. Thus, in contrast to high level exposure, which produced the Yusho syndrome in Japan, chronic low level exposure may be associated with only one or another of the neonatal deficits. The total impact of a toxin at these relatively low levels of exposure is, therefore, best estimated in a multiple regression analysis which includes a variety of potential adverse outcomes. In the present study, such an analysis indicates that 11.4% of the variance in contaminated fish consumption is associated with measureable neonatal deficits. Follow-up assessments of the affected infants are necessary to establish whether these deficits are transitory or whether they signal the onset of a toxic process that may impair subsequent cognitive and emotional development.

Footnotes

[1]School of Public Health, University of Michigan, Ann Arbor, Michigan 48109.

[2]Department of Psychology, Wayne State University, Detroit, Michigan 48202.

[3]Since the fish consumption interviews were not conducted by the same persons who subsequently collected medical and behavioral data, those engaged in assessment activities were blind with respect to the mothers' pattern of fish consumption and infants' potential exposure levels.

[4]Results of a state-wide survey of breast milk found PCB levels exceeding 2 mg/kg (fat basis) in 27 percent of the counties in the western part of the lower peninsula, in contrast to only 5 percent of the eastern counties (Wickizer, Brilliant, Copeland & Tilden, 1981). Grand Rapids is the largest metropolitan area located near Lake Michigan. The Grand River connects it to the lake and a fish ladder has made Grand Rapids a popular location for lake trout and spawning salmon. Muskegon is located directly on Lake Michigan.

[5]Data from the infant medical records were used to assign infants at-risk scores based on questions from the Postnatal Complications Scale (PCS) (Littman & Parmelee, 1974b). The PCS is based on 10 items considered to reflect increased risk of mortality and morbidity to newborns, such as respiratory distress, infection, hyperbilirubinemia, and metabolic and temperature disturbances. The PCS used an optimal scoring technique, such that high scores indicate few complications.

[6]If the father was a student, his father's education and occupation were used to estimate the family's socioeconomic status. In those cases in which the mother was unmarried, socioeconomic status was based on the occupation and education of the individual from whom the family was receiving most of its financial support.

[7]Data from the maternal interview and medical records are used to assign mothers at-risk scores based on 41 questions in the Obstetrical Complications Scale (OCS) (Littman & Parmelee, 1974a). The OCS score is derived from data relating to pregnancy, such as maternal infection, bleeding, parity, age; the reproductive history, such as previous premature births or stillbirths; and the delivery, such as obstetric medication, duration of labor, type of delivery, and birth weight. Like the PCS, the OCS is based on optimal scoring with high scores reflecting few complications.

[8]Lake Michigan was the primary source of fish. In addition, coho and chinook salmon and lake trout from rivers and lakes connected to Lake Michigan were included since these fish are normal inhabitants from the lake populations.

[9]The qualification rate of 4 per cent of the population screened, coupled with demographic data on the 18 Michigan counties adjacent to Lake Michigan, suggests that almost 100,000 women in this region might qualify as moderate fish-eaters. These figures do not include women in nearby Wisconsin, or from the Chicago area.

[10]The summary of the laboratory techniques used to analyze the serum and breast milk samples were written in conjunction with Dr. Harold A. Price of the Michigan Department of Public Health.

[11]A stricter criterion was applied to the reflex cluster. More than four abnormal reflexes were required, rather than three.

References

Abe, S., Inoue, Y., & Takamatsu, M. Polychlorinated biphenyl residues in plasma of Yusho chldren born to mothers who had consumed oil contaminated by PCB. Acta Medica Fukuoka, 1975, 66, 605-609.

Akiyama, K., Fujitani, K., Ohi, G., & Yagyu, H. Polychlorinated biphenyl residues in maternal and cord blood in Tokyo metroppolitan area. Bulletin of Environmental Contamination and Toxicology, 1975, 14, 588-592.

Aleksandrowicz, N. K. & Aleksandrowicz, D. R. Obstetrical pain-relieving drugs as predictors of infant behavior variability. Child Development, 1974, 45, 935-945.

Aleksandrowicz, N. K., & Aleksandrowicz, D. R. Precursors of ego in neonates: Factor analysis of Brazelton Scale data. Journal of the American Academy of Child Psychiatry, 1976, 15, 257-268.

Allen, J. R., Barsotti, D. A., & Carstens, L. A. Residual effects of polychlorinated biphenyls on adult nonhuman primates and their offspring. Journal of Toxicology and Environmental Health, 1980, 6, 55-66.

Als, H., Tronick, E., Lester, B. M., & Brazelton, T. B. Specific neonatal measures: The Brazelton Neonatal Behavioral Assessment Scale. In J. Osofsky (Ed.), Handbook of Infant Development. New York: Wiley, 1979.

Ballard, J. L., Novak, K. K., & Driver, M. A simplified score for assessment of fetal maturation of newly born infants. The Journal of Pediatrics, 1979, 95(5), 769-774.

Barr, H. M., Streissguth, A. P., Martin, D. C., & Horst, T. E. Methodological issues in assessment of caffeine intake: A method for quantifying consumption and a test-retest reliability study. In L. F. Soyka & G. P. Redmond (Eds.), Drug metabolism in the immature human. New York: Raven, 1981.

Biros, F. J., Walker, A. C., & Medbery, A. Polychlorinated biphenyls in human adipose tissue. Bulletin of Environmental Contamination and Toxicology, 1970, 5, 317-323.

Bowman, R. E., & Heironimus, M. P. Hypoactivity in adolescent monkeys perinatally exposed to PCBs and hyperactive as juveniles. Neurobehavioral Toxicology and Teratology, 1981, 3, 15-18.

Bowman, R. E., Heironimus, M. P., & Allen, J. R. Correlation of PCB body burden with behavioral toxicology in monkeys. Pharmacology, Biochemistry, and Behavior, 1978, 9, 49-56.

Brazelton, T. B. Neonatal Behavioral Assessment Scale. Philadelphia: Lippincott, 1973.

Burse, V. W., Needham, L. L., Liddle, J. A., Bayse, D. O., & Price, H. A. Interlaboratory comparison for results of analyses for polybrominated biphenyls in human serum. Journal of Analytical Toxicology, 1980, 4, 22-26.

Carey, A. E., & Gowen, J. A. PCB's in agricultural and urban soil. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975, EPA-560/6-75-004. Washington D.C., Environmental Protection Agency, 1976, 195-198.

Chia, L., Su, M., Chen, R., Wu, Z., & Chu, F. Neurological manifestations in polychlorinated biphenyls (PCB) poisoning. Clinical Medicine (Taipai), 1981, 7, 45-61.

Chou, S. M., Miike, T., Payne, W. M., & Davis, G. J. Neuropathology of "spinning syndrome" induced by prenatal intoxication with a PCB in mice. Annals of the New York Academy of Sciences, 1979, 320, 373-395.

DiVitto, B., & Goldberg, S. The effects of newborn medical status on early parent-infant interaction. In T. Field, A. Sostek, S. Goldberg, & H. Shuman (Eds.), Infants Born at Risk. Holliswood, NY: Spectrum, 1979.

Dubowitz, L. M., Dubowitz, V., & Goldberg, C. Clinical assessment of gestational age in the newborn infant. The Journal of Pediatrics, 1970, 77(1), 1-10.

Everett, D. EPA to limit toxaphene use. Detroit Free Press, October 19, 1982, 3; 8.

Field, T. M., Dabiri, C., Hallock, N., & Shuman, H. H. Developmental effects of prolonged pregnancy and the postmaturity syndrome. Journal of Pediatrics, 1977, 90, 836-839.

Field, T. M., Dempsey, J. R., & Shuman, H. H. Developmental follow-up of pre- and post-term infants. In S. L. Friedman & M. Sigman (Eds.), Preterm birth and psychological development. New York: Academic, 1981.

Field, T., Hallock, N., Ting, G., Dempsey, J., Dabiri, C., & Shuman, H. H. A first-year follow-up of high-risk infants: formulating a cumulative risk index. Child Development, 1978, 49, 119-131.

Fringe, C. S., Fendley, T. W., Dunn, R. T., & Queen, C. A. Improved determination of total serum lipids by the sulfo-phospho-vanillin reaction. Clinical Chemistry, 1972, 18, 673-674.

Funatsu, I., Yamashita, F., Ito, Y., Tsugama, S., Funatsu, T., Yoshikane, T., Hayashi, M., Kato, T., Yakushiji, M., Okamoto, G., Yamasaki, S., Arima, T., Kuno, T., Ide, H., & Ibe, I. Polychlorbiphenyls (PCB)-induced fetopathy. Kurume Medical Journal, 1972, 19, 43-51.

Gilbert, R. M., Marshman, J. A., Schwieder, M., & Berg, R. Caffeine content of beverages as consumed. Canadian Medical Association Journal, 1976, 114, 205-208.

Grant, D., Mes, J., & Frank, R. PCB residues in human adipose tissue and milk. National Conference on Polychlorinated Biphenyls, November 19-21, 1975, Chicago, Illinois. NTIS PB-253-248, 1976, 144-146.

Grant, D. L., Villeneuve, D. C., McCully, K. A., & Phillips, W. Placental transfer of polychlorinated biphenyls in the rabbit. Environmental Physiology, 1971, 1, 61-66.

Harada, M. Intrauterine poisoning. Clinical and epidemiological studies and significance of the problem. Bulletin of the Institute of Constitutional Medicine, Kumamoto University, 1976, 25(Suppl.).

Higuchi, K. (Ed). PCB Poisoning and Pollution. New York: Academic Press, 1976.

Hirayama, C. Clinical aspects of PCB poisoning. In K. Higuchi (Ed.), PCB Poisoning and Pollution. New York: Academic Press, 1976.

Hollingshead, A. B. Four factor index of social status. Unpublished manuscript, Yale University, New Haven, n.d.

Humphrey, H. E. B. Evaluation of changes of the level of polychlorinated biphenyls (PCB) in human tissue. Unpublished manuscript, Michigan Department of Public Health, Lansing, 1976.

Horowitz, F. D., Sullivan, J. W., & Linn, P. Stability and instability in the newborn infant: The search for elusive threads. In A. J. Sameroff (Ed.), Organization and stability of newborn behavior: A Commentary on the Brazelton Neonatal Behavioral Assessment Scale. Monographs of the Society for Research in Child Development, 1978, 43(5-6, Serial No. 177).

International Agency for Research on Cancer. Polychlorinated biphenyls and polybrominated biphenyls. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 1978, 18.

International Joint Commission, Great Lakes Water Quality Board: Appendix E. Status report on organic and heavy metal contaminants in the Lakes Erie, Michigan, Huron and Superior basins, 1978.

Jacobson, J. L., Fein, G. G., Jacobson, S. W., & Schwartz, P. M. Factors and clusters for the Brazelton Scale: An investigation of the dimensions of neonatal behavior. Developmental Psychology, in press.

Jacobson, S. W., Jacobson, J. L., Schwartz, P. M., & Fein, G. G. Intrauterine exposure of human newborns to PCBs: Measures of exposure. In F. M. D'Itri & M. Kamrin (Eds.), PCBs: Human and environmental hazards. Ann Arbor: Ann Arbor Science, in press.

Jelinek, C. F., & Corneliussen, P. E. Levels of PCBs in the US food supply. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, November 19-21, 1975, EPA-560/6-75-004. Washington, D.C.: Environmental Protection Agency, 1976, 147.

Kaye, K. Discriminating among normal infants by multivariate analysis of Brazelton scores: Lumping and smoothing. In A. J. Sameroff (Ed.), Organization and stability of newborn behavior: A commentary on the Brazelton Neonatal Behavioral Assessment Scale. Monographs of the Society of Research in Child Development, 1978, 43(5-6, Serial No. 177).

Kenny, D. A. Correlation and causality. New York: Wiley, 1979.

Kodama, H., & Ota, H. Studies on the transfer of PCB to infants from their mothers. Japanese Journal of Hygiene, 1977, 32, 567-573.

Kodama, H., & Ota, H. Transfer of polychlorinated biphenyls to infants from their mothers. Archives of Environmental Health, 1980, 35, 95-100.

Kreiss, K., Zack, M. M., Kimbrough, R. D., Needham, L. L., Smrek, A. L., & Jones, B. T. Association of blood pressure and polychlorinated biphenyl levels. Journal of the American Medical Association, 1981, 245, 2505-2509.

Kuwabara, K., Yakushiji, T., Watanabe, I., Yoshida, S., Koyama, K., & Kunita, N. Levels of polychlorinated biphenyls in blood of breast-fed children whose mothers are non-occupationally exposed to PCBs. Bulletin of Environmental Contamination and Toxicology, 1979, 21, 458-462.

Kuzma, J. W., & Kissinger, D. G. Patterns of alcohol and cigarette use in pregnancy. Neurobehavioral Toxicology and Teratology, 1981, 3, 211-221.

Lester, B. M., Als, H., & Brazelton, T. B. Regional obstetric anesthesia and newborn behavior: A reanalysis toward synergistic effects. Child Development, 1982, 53, 687-692.

Liddle, J. A. Interlaboratory comparability of serum PCB analyses. In F. M. D'Itri & M. Kamrin (Eds.), PCBs: Human and environmental hazards. Ann Arbor: Ann Arbor Science, in press.

Littman, B., & Parmelee, A. H. Manual for obstetrical complications. Unpublished manuscript, University of California, Los Angeles, 1974a.

Littman, B., & Parmelee, A. H. Manual for postnatal complications. Unpublished manuscript, University of California, Los Angeles, 1974b.

Lubchenco, L. O., Hansman, C., Dressler, M., & Boyd, E. Intrauterine growth as estimated from live-born birthweight data at 24 to 42 weeks of gestation. Pediatrics, 1963, 32, 793-800.

Masuda, Y., Kagawa, R., Kuroki, H., Kuratsune, M., Yoshimura, T., Taki, I., Kusuda, M., Yamashita, F., & Hayashi, M. Transfer of polychlorinated biphenyls from mothers to foetuses and infants. Bulletin of Environmental Contamination and Toxicology, 1978, 16, 543-546.

Masuda, Y., Kagawa, R., Kuroki, B., Tokudome, S., & Kuratsune, M. Transfer of various polychlorinated biphenyls to the foetuses and offspring of mice. Food and Cosmetic Toxicology, 1979, 17, 623-627.

Matthews, H. B. The metabolism of PCBs in mammals. In F. M. D'Itri & M. Kamrin (Eds.), PCBs: Human and environmental hazards. Ann Arbor: Ann Arbor Science, in press.

Miller, H. C., & Hassanein, K. Diagnosis of impaired fetal growth in newborn infants. Pediatrics, 1971, 48(4), 511-522.

Mullin, M., Safe, S., Safe, L., Pochini, C., McCrindle, S., & Romkes, M. Analysis of PCBs using specific isomer high resolution capillary gas chromatography. In F. M. D'Itri & M. Kamrin (Eds.), PCBs: Human and environmental hazards. Ann Arbor: Ann Arbor Science, in press.

Musial, C. J., Hutzinger, O., Zitko, V., & Crocker, J. Presence of PCB, DDE and DDT in human milk in the provinces of New Brunswick and Nova Scotia, Canada. Bulletin of Environmental Contamination and Toxicology, 1974, 12, 258.

Needham, L. L., Burse, V. W., & Price, H. A. Temperature-programmed gas chromatographic determinations of polychlorinated and polybrominated biphenyls in serum. Journal of Association of Official Analytical Chemists, 1981, 64, 1131-1137.

Osofsky, J. D., & O'Connell, E. J. Patterning of newborn behavior in an urban population. Child Develoment, 1977, 48, 532-536.

Picer, M., & Ahel, M. Separation of polychlorinated biphenyls from DDT and its analogues on a miniature silica gel column. Journal of Chromatography, 1978, 150, 119-127.

Polishuk, Z. W., Wasserman, D., Wasserman, M., Cucos, S., & Ron, M. Organochlorine compounds in mother and fetus during labor. Environmental Research, 1977, 13, 278-284.

Powell, L. F. The effect of extra stimulation and maternal involvement on the development of low-birth-weight infants and on maternal behaviors. Child Development, 1974, 45, 106-113.

Sameroff, A. J., Krafchuk, E. E., & Bakow, H. A. Issues in grouping items from the Neonatal Behavioral Assessment Scale. In A. J. Sameroff (Ed.), Organization and stability of newborn behavior: a commentary on the Brazelton Neonatal Behavioral Assessment Scale. Monographs of the Society for Research in Child Development, 1978, 43(5-6, Serial No. 177).

Savage, E. P., Tessari, J. D., Malberg, J. W., Wheeler, H. W., & Bagley, J. R. A search for polychlorinated biphenyls in human milk in rural Colorado. Bulletin of Environmental Contamination and Toxicology, 1973, 12, 258.

Sawyer, L. D. Quantitation of polychlorinated biphenyl residues by electron capture gas-liquid chromatography. Journal of Association of Official Analytical Chemists, 1978, 61, 272-291.

Spyker, J. M. Assessing the impact of low-level chemicals on development: Behavioral and latent effects. Federation Proceedings, 1975, 34(9), 1835-1844.

Storm, J. E., Hart, J. L., & Smith, R. F. Behavior of mice after pre- and postnatal exposure to Arochlor 1254. Neurobehavioral Toxicology and Teratology, 1981, 3, 5-9.

Strauss, M. E., Lessen-Firestone, J. K., Starr, R. H., Jr., & Ostrea, E. M., Jr. Behavior of narcotics-addicted newborns. Child Development, 1975, 46, 887-893.

Streissguth, A. P., Martin, D. C., & Barr, H. M. Factor structure of the Brazelton Neonatal Behavioral Assessment Scale and experimental design considerations for the use of the Brazelton for outcome research. Paper presented at the meetings of the American Psychological Association, San Francisco, 1977.

Swain, W. R. An ecosystem approach to the toxicology of residue forming xenobiotic organic substances in the Great Lakes. In Ecotoxicology working papers: Testing for the effects of chemicals on ecosystems. Washington, D.C.: National Academy of Sciences, 1981.

Tilson, H. A., Davis, G. J., McLachlan, J. A., & Lucier, G. W. The effects of polychlorinated biphenyls given prenatally on the neurobehavioral development of mice. Environmental Research, 1979, 18, 466-474.

Torok, P., & Weber, L. W. Distribution of polychlorobiphenyls in pregnant mice and fetuses on various days of gestation. Archives of Environmental and Contamination Toxicology, 1981, 10, 289-296.

Vaughn, B., Taraldson, B., Crichton, L., & Egeland, B. Relationships between neonatal behavioral organization and infant behavior during the first year of life. Infant Behavior and Development, 1980, 3, 47-66.

Veith, G. D., & Lee, G. F. Polychlorinated biphenyls (PCBs) in the Milwaukee River. Water Research, 1971, 5, 1107-1115.

Webb, R. G., & McCall, A. C. Quantitative PCB standards for electron capture gas chromatography. Journal of Chromatographic Science, 1973, 11, 366-373.

Wickizer, T. M., Brilliant, L. B., Copeland, R., & Tilden, R. Polychlorinated biphenyl contamination of nursing mothers' milk in Michigan. American Journal of Public Health, 1981, 71, 132-137.

Willford, W. A., Hesseburg, R. J., & Nicholson, L. W. Trends in polychlorinated biphenyls in three Lake Michigan fishes. In: Proceedings of the National Conference on Polychlorinated Biphenyls. Washington, D.C.: Environmental Protection Agency, 1976.

Wong, K. C., & Hwang, M. Y. Children born to PCB poisoned mothers. Clinical Medicine (Taipei), 1981, 7, 83-87.

Yobs, A. R. Levels of polychlorinated biphenyls in adipose tissue of the general population of the nation. Environmental Health Perspectives, 1972, 1, 79-81.

Yoshimura, H., & Yoshimura, S. Toxicological aspects II: the metabolic fate of PCB's and their toxicological evaluation. In K. Higuchi (Ed.), PCB Poisoning and Pollution. New York: Academic Press, 1976.

Young, D. R., McDermott, D. J., & Heesen, T. C. Marine inputs of polychlorinated biphenyls off Southern California. In: Proceedings of the National Conference on Polychlorinated Biphenyls, Chicago, 1975, EPA-560/6-75-004. Washington D.C., Environmental Protection Agency, 1976, 199-208.